JUN 13 1961

volume 22
number 5
may 1961

Diseases of the Nervous System

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Section Two - Supplement

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SYMPOSIUM ON DEPRESSION

with Special Studies of a New Antidepressant, Amitriptyline

A SCIENTIFIC MEETING

Held Under the Auspices of

EASTERN PSYCHIATRIC RESEARCH ASSOCIATION

NEW YORK, N. Y.

MARCH 4, 1961

Published by
PHYSICIANS POSTGRADUATE PRESS
277 BROADWAY - NEW YORK 7, NEW YORK

DISEASES *of the* Nervous System

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Mental Depressions

WILLIAM L. HOLT, JR., M.D.

Depression of mood is a combination of incapacity for enjoyment of healthy activity and a pessimistic expectation of its continuance. It may be an accompaniment of structural or physiologic change (bodily disease), or an apparently primary mood change unrelated to external events or their effects upon a person's system of values and self-concepts, or directly related to the external stress. When it is the latter, we call the condition a "reaction."

Rather than a symptom of disease, mild brief mood depression is normal. Its intensity forms a continuum which at one end is normal and at the other end is a major illness, rendering the sufferer incapable of caring for himself or herself and requiring outside assistance to preserve life itself. The duration of untreated depressive reactions is highly variable, many disappearing in a few days, and a few persisting for decades. Variations in intensity and duration are common to the three etiologic groups of depression. All show capacity for recurrence when the etiologic determinant recurs. Influenza has a relatively high incidence of mood depression as does myxedema, infectious hepatitis, undulant fever and mononucleosis. It is not uncommon in certain stages of tuberculosis, poliomyelitis, malignancy, extensive burns, amputation, cataract sufferers, and organic brain disorders.

Patients to whom the external environmental stress is of major importance are classified as mild (normal), moderately incapacitated (neurotic depressive reaction) and severe (psychotic depressive reaction). They are to be distinguished from patients with depression of the endogenous or constitutional type, the Manic Depressive patient and patients with Involutional Disorders. The latter have, as yet, no clearly defined physical basis on structural change in the brain, but as in schizophrenia, concomitant physiologic changes are found during the psychotic reactions, and genetic constitutional tendency to a specific pattern of mental breakdown has been established.

Unfortunately, our nomenclature as revised in 1952, has overemphasized the importance of presence or absence of a history of repeated depressions. A second depression, therefore, usually places the case in the Manic Depressive Reaction group even though external stress is great, and genetic trait liability minimal. The differentiation between a neurotic and a psychotic depressive reaction is based upon the severity of a first depression. A psychosis is present in one and absent in the other. A depressive psychosis may be defined operationally as such a degree of change in thought, feeling and behavior as to require care in a protective environment because the psychotic person can no longer care for himself and would be liable to inflict harm on himself or others, usually because of the severity of the depression and misinterpretation of reality. Somatic delusions, ideas of reference, anorexia, insomnia, extreme fatigue, ideas of guilt and a wish to die are commonly present.

The Manic Depressive Reaction is characterized by a positive family history of this disorder, repeated attacks, a cyclothymic prepsychotic personality and severe mood swings. Elevated mood episodes are pathognomonic when found. The Involutional Psychotic Reaction is a first attack of psychosis in the age group 40 to 70 without demonstrable brain changes, or toxic factors. Depression, agitation, misinterpretation of reality, somatic preoccupation, anorexia, insomnia, menopause and a prolonged course (when untreated) characterize this disorder. The prepsychotic personality is often a rigid compulsive one. The differentiation from the Psychotic Depressive Reaction is often difficult, as external stress may be a significant factor and is commonly present to some degree throughout this age period.

Depression may be present in a wide variety of other mental disorders such as alcoholism, epilepsy, mental deficiency, schizophrenia, or the personality disorders. In the latter, relationships with other people are subject to brief, stress-induced moods, including depression, because of poorly controlled hostility, anxiety and guilt.

Incidence of Depressive Reactions. The incidence of depressive reactions is lowest in

institutions with predominantly chronic, stable populations, and highest in the acute services of general hospitals. In 1950, statistics on 100,223 first admissions to State Hospitals, showed the incidence of manic depressive psychosis to be 5.2%. The incidence of Involutional Psychotic Reactions was 4.9%. All psychoneuroses were 4.6%. In New York State, the incidence of Involutional Psychotic Reactions was 6.8% and Manic Depressive Psychosis 2.3%. This latter figure is only 17% of the admission rate in the same state 22 years earlier, leading some psychiatrists to state it is a disappearing psychosis.

That these depressive disorders are not disappearing, but being spared State Hospital admission, is strongly suggested by the experience of the Psychiatric Department of Albany Medical Center Hospital. Other general hospital treatment units can no doubt duplicate the figures below.

ALBANY MEDICAL CENTER HOSPITAL
PSYCHIATRY DEPT.—1960 ADMISSIONS

Total Admissions 1703: Male 640, Female 1063

	%	No.	%	No.
Involutional Psychotic Reaction	8%	51	11%	112
Manic Depressive Reaction, Depressed	7%	44	12%	124
Psychotic Depressive Reaction	3.1%	20	3.5%	36
Neurotic Depressive Reaction	5.3%	34	7.7%	78
Emotionally Unstable Personality with Depression	1.6%	10	4.6%	47
Total Depressive Reactions Above	25.0%	159	38.8%	397
Total Male and Female Depressive Reactions	% of Admissions 32.8%			

The above figures do not include depressions accompanying other mental disorders or physical disease. The latter patients are not statistically identifiable without an examination of each record in detail. It is my belief that the majority of psychiatric patients admitted to Albany Medical Center Hospital suffer symptoms of depression, and treatment is aimed at relief of this symptom.

The incidence of depression in office psychiatric practice is about the same as for general hospital admissions if the practitioner is doing general psychiatry. Those psychiatrists doing electroshock therapy will have a greater number of patients with psychotic depression. Psychotherapists who rarely use somatic therapy will see fewer patients with severe depression.

The recognition of depression is as important as the recognition of pulse irregularity or an acute abdomen, and the proper handling of it is just as difficult. A good interviewing technique which never omits a search for signs of depression is essential. Sleep changes, changes in ability to enjoy interests, in food, recreation, health, sex and work are important leads. Has the person begun to put financial affairs in order for the final eventuality? If so, death has undoubtedly become a preoccupation and serious depression can reasonably be inferred even where denied. Somatic preoccupation, hostility, irritability, restlessness, weight loss, fatigue, and withdrawal also may be due to depression. Where tears and admitted despondency are seen, the diagnosis is simple, but a search for toxic and organic factors may be essential before a proper treatment plan can be made. Protection of the life of the patient from suicide must be the first duty of the physician. Sleeplessness and "accidents" are not to be ignored and, above all, take suicidal preoccupation as seriously as you would the actual attempt.

Albany, N. Y.

The Pharmacology of Antidepressant Agents

VERNON G. VERNIER, M.D.

During the current decade the armamentarium of the psychiatrist for dealing with depressed patients has increased to the extent that it now begins to approach in number the agents which can deal with psychomotor agitation. This development began with the observation in 1951 that a prospective antituberculosis chemical caused euphoria, improved attitudes and appetite in depressed patients.[1] Subsequently it was reported that this drug, iproniazid, markedly inhibited an important enzyme, monoamine oxidase.[2] It is now clear that the antidepressants may be separated into two pharmacological classes, those that do and those that do not inhibit monoamine oxidase.

I. Monoamine Oxidase Inhibitors

The first group comprises the "psychic energizers" or more precisely, the monoamine oxidase inhibitors. The structures of the chief compounds in this group are shown in Figure 1. Chemically they are all amines, hydrazines, or hydrazides. The three agents on the left contain a phenylethylamine nucleus which relates them to the pressor amines.

This class of drugs has shown clinical utility in psychiatry for the relief of depressive states and has also been used for hypertension, angina, and rheumatoid arthritis. Their major pharmacological actions are outlined in Table I. The behavioral effects are in marked contrast to the stimulation of amphetamine in intesity and time course. In animals amphetamine elicits obvious hyperactivity immediately after injection, while monoamine oxidase inhibitors often cause depresson.[3,4] In fact, the only laboratory test which appears to provide an analog of their clinical antidepressant action is that of Irwin,[5] who reported that chronic iproniazid treatment maintained the activity of rats running in exercise wheels at higher levels than controls.

The biochemical activity of this group is exerted upon monoamine oxidase, a widely distributed enzyme occurring chiefly in liver, kidney and gut, but also present in brain and heart. Monoamine oxidase converts an aliphatic amine to a carbonyl residue. Its substrates include tyramine, tryptamine, serotonin and catecholamines, including dopamine, norepinephrine and epinephrine.[6]

Monoamine oxidase inhibitors have the predominant capability of preventing the *in vitro* oxidation of these biological amines. Pretreatment of laboratory animals with these enzyme inhibitors reduces the monoamine oxidase activity in liver, brain or heart in the extracted organs.[7] Numerous laboratories have now confirmed the original observation that brain serotonin concentra-

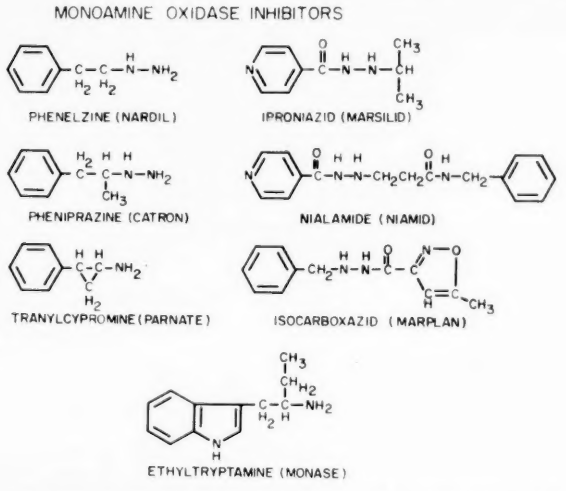

Figure 1. Chemical structures of monoamine oxidase inhibitors.

From Merck Institute for Therapeutic Research, West Point, Pennsylvania.

TABLE I

Major Pharmacological Actions of Monoamine Oxidase Inhibitors

Inhibit monoamine oxidase
- in vitro, in vivo
- increase brain serotonin, norepinephrine, etc.
- increase susceptibility to tryptamine convulsions
- increase tryptamine urinary output in man
- decrease 5-HIAA urinary output in man

Prevent reserpine and tetrabenazine sedation
Potentiate 5-HTP and DOPA excitement
Increase motor activity chronically
Anticonvulsant effect—electroshock and pentylenetetrazole
Prolong hexobarbital righting reflex loss
Toxic actions on liver and blood
Decrease cardiovascular reflexes—carotid occlusion, tilt

tion rose after monoamine oxidase inhibitor administration.[8,9] This phenomenon has been used as a screening test for potential antidepressants. A rise in brain norepinephrine often follows treatment with these antidepressants along with changes in other amines. Thus, the exogenous tryptamine required to cause convulsions is reduced following dosing with monoamine oxidase inhibitors.[10]

Successful attempts have been made to measure monoamine oxidase activity in man. Sensitive assay methods indicate that useful monoamine oxidase inhibitors raise human urinary tryptamine output and that this capacity of drugs tends to correlate with the recommended antidepressant dose and the production of orthostatic hypotension.[11] Serotonin, given orally to man, is oxidized to 5-hydroxyindoleacetic acid, which can be measured in the urine. Monoamine oxidase inhibitor treatment markedly decreases urinary 5-hydroxyindoleacetic acid, which provides another index of drug action.[12] However, these agents affect other enzyme systems, and the importance of those actions must also eventually be clarified.

Pretreatment of laboratory animals with monoamine oxidase inhibitors prevents the sedative action of reserpine[13] and of a synthetic congener, tetrabenazine,[14] and may even convert them into a state of excitation. Additionally, monoamine oxidase inhibitors increase the excitement of animals given the serotonin and norepinephrine precursors, 5-hydroxytryptophan and dihydroxyphenylalanine.[15-17]

The significance of the anticonvulsant effect of these drugs against electroshock and pentylenetetrazole is not yet clear.[3,18,19] Monoamine oxidase inhibitors inhibitors prolong the anesthesia of hexobarbital in mice and also the effects of other drugs, probably by interference with the liver enzymes which terminate their action, but this action is not correlated with monoamine oxidase inhibition.[3,20-22]

Explanations have been sought for the other therapeutic actions of monoamine oxidase inhibitors. They have been alleged to reduce cardiovascular reflexes, including the pressor response to carotid occlusion[23] and compensatory changes in tilt table experiments, providing a foundation for the clinical orthostatic hypotension.[3] Reduction in experimental hypertension has been noted.[24] Some workers have described an analgesic action of iproniazid which might explain the antianginal phenomenon.[25,26] This enumeration completes the list of the more important pharmacological actions of the monoamine oxidase inhibitors.

II. Non-Monoamine Oxidase Inhibitors

More recently a new class of effective antidepressant agents has become available which is structurally unrelated to the hydrazides and which does not inhibit monoamine oxidase. The two members of this group of antidepressants bear some chemical resemblance to each other and also to the phenothiazines. Their structures are given in Figure 2. Amitriptyline is 5-(3-dimethylaminopropylidene)-dibenzo[a, d][1, 4] cycloheptadiene hydrochloride. In imipramine the central seven-membered ring is azepine, the nitrogen replacing the partially unsaturated carbon of the amitriptyline cycloheptadiene ring. Thus, imipramine is chemically 10, 11-dihydro-5-(3-dimethylaminopropyl) - 5H-dibenzo[b, f]azepine hydrochloride. Amitriptyline, a new agent, was synthesized by chemists of the Merck Sharp & Dohme Research Laboratories. Results which are presently available from the extensive clinical trials under way, indicate that amitriptyline possesses a high degree of efficacy and safety in psychiatric depressions of various types.[27,-29] The following results reveal that amitriptyline displays a variety of pharmacodynamic attributes.

A. Electroencephalographic Effects. The central nervous system effects were studied through its actions upon the EEG and behavior of cats and monkeys. In unanesthetized cats (paralyzed with gallamine and respired artificially) incremental intravenous doses caused a slowing of the spontaneous electrical activity in the range of 0.2 mg./kg.

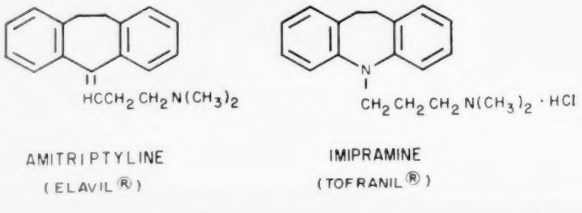

Figure 2. Chemical structures of non-monoamine oxidase inhibitors.

Moderate doses often caused attenuation of alerting responses evoked by loud tones and foot pinches. Dosage of 7-10 mg./kg. resulted in the absence of EEG activation following tone and pinch. These quantitative results are illustrated in Figure 3 and compared with those of chlorpromazine and scopolamine. The points represent the cumulative dosage required to achieve the EEG effects listed on the ordinate. The effects of amitriptyline and chlorpromazine are generally similar, the latter being about 3.5 times more potent, while the dose response curves appear to be parallel. Scopolamine shows much greater potency and a considerably steeper response curve. All three drugs have a depressant action upon the cat EEG, amitriptyline being the least active. Similar EEG effects have been reported for imipramine.[30-32]

Further EEG studies were carried out upon rhesus monkeys with chronically implanted cortical electrodes. The monkeys were trained to avoid a foot pinch on a modified Sidman avoidance schedule. They pressed a lever delaying the auditory warning stimulus, terminating the stimulus or removing the pinch. The concurrent effects of amitriptyline on EEG and avoidance behavior revealed only a slight slowing of spontaneous brain waves and no change in behavior at 0.1 mg./kg. intravenously. After 1.0 mg./kg. a more pronounced slowing of spontaneous EEG activity was detected, the activation evoked by the warning stimulus was delayed and shorter and the average rate of responding showed a slight increase which may have been evidence of a disruptive effect. A high dose of 3.0 mg./kg. produced, in addition to definite spontaneous EEG slowing, marked loss of EEG arousal to the warning clicker, and some diminution of electrographic response to pinch. Behavior was markedly affected with definite increase in response latency and lowering of response rate, with the monkeys receiving pinches for failing to respond to the auditory warning. Some of the animals showed EEG arousal and escaped by lever pressing when the pinch was applied. The remainder showed less EEG arousal and did not escape the pinch. The alerting pattern to pinch was not abolished. The actions of amitriptyline appeared generally similar to those of chlorpromazine on EEG and avoidance behavior, being about 1/3 as potent. Imipramine exerted a similar combination of effects on EEG and behavior. At 0.1 to 3.5 mg./kg. it caused slowing of spontaneous EEG activity and attenuation of click activation responses. In some of the monkeys imipramine caused an increase in lever pressing rate, while showing a slow EEG pattern. The eyes were usually closed but opened when a response was made. This could be interpreted as a mild sedative effect, with disruption of the monkey's trained pattern of responding. The other monkeys showed only moderate effects of imipramine on avoidance behavior. This drug at 7.0 mg./kg. slowed spontaneous EEG activity,, abolished click and pinch activation, lowered avoidance rate and abolished escape. Thus imipramine was generally similar in action to chlorpromazine and amitriptyline, and was considerably less potent than the former and slightly less active than the latter. Both amitriptyline and imipramine showed instances of increased rate of lever pressing on avoidance which might be indicative of a central nervous system antichol'nergic action, since this type of change was much less prominent with chlorpromazine but was noted with scopolamine.[33]

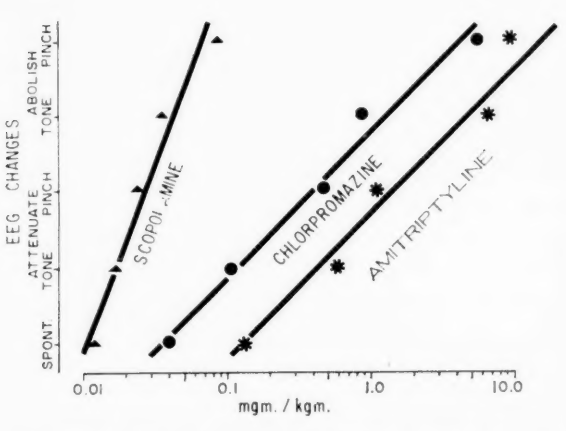

Figure 3. Effects of amitriptyline on the cat EEG. Abscissa represents geometric mean cumulative dose in mg./kg. intravenously required to exert the effects listed on the ordinate, namely, slowing of spontaneous activity, attenuation of alerting response or abolition of alerting response, by scopolamine (n = 6 cats), chlorpromazine (n = 6 cats) and amitriptyline (n = 4 cats).

B. Behavioral Effects. Amitriptyline and imipramine were studied for their effects upon operant behavior. The ability of squirrel monkeys to lever press on a Sidman avoidance schedule was tested following

three oral doses during each session. After 5.0 mg./kg. of amitriptyline, the response rate was minimally decreased and the number of shocks received rose slightly. The cumulative 10.0 mg./kg. dose markedly decreased responses and increased shocks. At the highest dose (20.0 mg./kg.) increased responding occurred, some shocks were taken and disruption of the desirable spacing of responses occurred in the form of short bursts of lever pressing. Imipramine caused depression of avoidance activity at the same doses, with the absence of response runs and disruption. Chlorpromazine, at 1.25, 2.5 and 5.0 mg./kg. orally, caused first a slight depression of avoidance rate, increased effect with higher doses, and finally loss of all avoidance and escape responding with no ataxia or apparent disruption of pattern. This action of chlorpromazine illustrates its four times greater potency than the two antidepressants, while amitriptyline differed from imipramine by the presence of the disruptant action at these high doses.[34]

The same drugs were also studied for effects upon food reinforced performance. Rats lever pressed on a chain schedule with a fixed interval component and a fixed ratio requirement, which generated a positively accelerated pattern of responding following a pause after each reward. Three cumulative oral doses were given, 40, 80 and 160 mg./kg. of the two antidepressants, and 5, 10 and 20 mg./kg. of chlorpromazine. Amitriptyline was without action after the first dose, caused decrease of overall rate with some disruption of the fixed interval "scallop" after the second, and complete cessation of responding at the high dose with loss of even the fixed ratio responses. Imipramine exerted no effect at the low dose, a slight decrease in rate after the second dose, and finally a marked drop in response rate at the high dose with some disruption of the fixed interval performance, but maintenance of the fixed ratio responding. Here the two antidepressants were essentially identical in type of depression of rat appetitive behavior, but amitriptyline was approximately twice as potent as imipramine. Chlorpromazine first decreased rates slightly, then markedly depressed rates, and finally abolished all responding after the highest dose, and thus was in the vicinity of eight times as potent as amitriptyline and presumably that much more capable of sedation.[34]

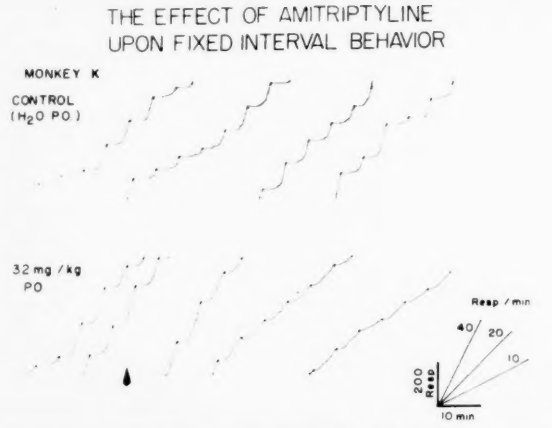

Figure 4. The effect of amitriptyline upon fixed interval behavior.

Behavioral actions of amitriptyline were confirmed in other species with other techniques. In Figure 4 is illustrated an effect upon the fixed interval responding of a rhesus monkey for food. The upper section is a control cumulative record. Every five minutes one reinforcement is delivered, marked by the downward deflection of the pen. The monkey consumes the food and pauses several minutes before responding at a positively accelerated rate. The lower panel shows that the effect of amitriptyline was first to increase the number of lever presses occurring in each interval during the first hour. The terminal rate was not increased but the post-reinforcement pause was moderately shortened so that the rising part of the curve began sooner. During the second hour the pause was nearly gone and the terminal rate was depressed. It is clear that the temporal discrimination was considerably disrupted. Imipramine was less potent in causing this depressant effect.[35]

C. Anticonvulsant Actions. Amitriptyline possessed considerable anticonvulsant activity, as reflected by an ability to modify the seizure pattern of electrically and pentylenetetrazole-induced convulsions in mice. Strychnine-induced convulsions were not influenced. These data are summarized in Table II. The anticonvulsant spectrum of amitriptyline resembled that of diphenylhydantoin, in that it was exerted only against the tonic extensor component of both electroshock- and pentylenetetrazole-induced maximal seizures.

TABLE II

Anticonvulsant Actions of Amitriptyline on Electroshock-, Pentylenetetrazole- and Strychnine-Induced Convulsions in Mice

Compound	Time of* Administration	Maximal Electroshock Convulsions** ED_{50}: mg./kg. I.P.	Maximal Pentylenetetrazole Convulsions† ED_{50}: mg./kg. I.P.	Strychnine Convulsions‡ ED_{50}: mg./kg. I.P.
Amitriptyline	30 min.	11.6	13.2	>80
Imipramine	30 min.	34.7	32.0	>50
Diphenylhydantoin	40 min.	11.4	13.1	60.1
Trimethadione	40 min.	1200	158	379

*Prior to carrying out the convulsive procedures.

**The method of Swinyard *et al.*[36] was employed. The ED_{50} is that amount required to prevent the appearance of the hind limb component of the convulsion in 50% of the mice and was based upon 5 doses, with 10 mice/level. The ED_{50}'s in this and other columns were calculated by the moving average method.

†The ED_{50} is that amount required to abolish the hind limb component that follows appropriate doses of pentylenetetrazole. The standard dose of the convulsant was 70 mg./kg., delivered I.V. rapidly. This dose of pentylenetetrazol produces full maximal seizures in 100% of untreated mice. The ED_{50} was based upon 4-5 doses with 10 mice at each level.

‡The ED_{50} represents that amount required to prevent death resulting from a standard dose of strychnine in 50% of the mice 30 minutes following its injection. The dose of strychnine employed was 0.77 mg./kg., intravenously, which in untreated animals causes death in 100% of the mice within 10 minutes after administration. The ED_{50} was based upon 10 mice at each of 4-5 dose levels.

Amitriptyline was about equiactive with diphenylhydantoin in modifying the seizures of either the electroshock or pentylenetetrazole procedures, and both were more active than trimethadione. Imipramine possessed anticonvulsant activity similar to that of amitriptyline, except that the latter was considerably more active and its effect was of greater duration.[37] The significance of the anticonvulsant action of amitriptyline and imipramine remains to be determined.

D. Hexobarbital Potentiaton. Amitriptyline was found to be capable of prolonging hexobarbital anesthesia in mice. At 40 mg./kg. I.P., the duration was increased to 5.5 times that of the control without prior sedation. Imipramine also prolonged hexobarbital anesthesia but was less active than amitriptyline. The mechanism of this effect is probably analogous to that of chlorpromazine in view of the weak depressant properties of both amitriptyline and imipramine.[37]

E. Brain Serotonin. The administration of amitriptyline (10 mg./kg. I.P.) once daily for three days did not result in a change in whole brain serotonin content (measured in mice by the method of Udenfriend *et al.*[38]). Imipramine, at a higher dose (25 mg./kg. I.P.) was also inactive. Thus the depressant action sometimes seen with these agents was probably not due to the mechanism responsible for the reserpine-induced depression which is thought to be mediated by the release of serotonin and/or other substances.[39]

F. Autonomic Effects. Amitriptyline, like imipramine,[40] was found to exert a variety of autonomic effects. These were classified as atropine-like, antihistaminic and antiserotonin actions. Atropine-like activity was manifested by moderate blockade of vasodepressor response to peripheral vagal stimulation and injected acetylcholine. Amitriptyline was about one-fiftieth as potent as atropine in dilating the mouse pupil. Imipramine was less active than amitriptyline in anticholinergic activity. Amitriptyline possessed considerable anti-histaminic action (dog vasodepression, isolated guinea pig ileum and guinea pig aerosol), while imipramine was much less active. Amitriptyline possessed weak specific antiserotonin activity (isolated rat uterus, dog blood pressure and rat paw edema), as did imipramine to a certain extent. While amitriptyline also caused some adrenergic blockade by blocking epinephrine pressor action, norepinephrine response was slightly increased.[37] Imipramine did not block epinephrine and caused a greater potentiation of norepinephrine, which has been described by Sigg.[30] Amitriptyline was essentially lacking in direct cardiovascular actions.[37]

G. Gastrointestinal Effects. Experiments with pylorus-ligated rats (Shay rat preparation) revealed a significant antisecretory action of amitriptyline. Examination of the gastric contents for volume, free acidity and total acidity revealed that amitriptyline was effective at an intraperitoneal dose of 16 mg./kg. and thus 1/5 as potent as atropine in reducing gastric secretion. Its action was predominantly upon gastric acidity and less upon volume of stomach contents.[33] This result suggested that amitriptyline might be useful in the therapy of peptic ulcer, and indeed, preliminary results from subsequent clinical trials appear to confirm this utility.

A possible antiulcer action has also been reported for imipramine.[41,42] The site and mode of action of this gastrointestinal activity of amitriptyline are yet to be elucidated, but they may be other than a peripheral anticholinergic effect.

H. Metabolism. A sensitive analytical method has been developed for the detection of amitriptyline.[43] Preliminary results of metabolic studies have revealed that amitriptyline was rapidly absorbed by dogs following oral administration. In the rabbit, following intravenous administration, plasma levels quickly rose and reached a peak at 30 minutes and then fell, no drug being detectible at 15 hours indicating rapid metabolism. Tissue distribution studies in rabbits indicated selective concentrations of amitriptyline, highest in lung, kidney, brain, spleen and heart. Biochemical alteration of amitriptyline by the body occurs by monodemethylation of the side chain nitrogen hydroxylation of the carbons of the central seven-membered ring, and glucuronide conjugaton. The metabolic transformations of imipramine are similar, but Hermann and Pulver[44] have reported monohydroxylation of the benzene rings.

Discussion

This review of antidepressant therapy has attempted to develop clues to the mode of action of the useful drugs. The evidence for the basic mechanism of action of the monoamine oxidase inhibtors appears to rather closely associate this enzyme inhibition with the cause of the clinical antidepressant effect and other therapeutic actions.[11,21,45]

With the non-monoamine oxidase inhibitors there is no reasonable evidence for mode of action. Two general possibilities seem relevant at the present time. Sigg has proposed that imipramine exerts its antidepressant action by sensitization of the central nervous system to the actions of adrenergic neurohumoral transmitters, especially norepinephrine.[30] He has reasoned that since the peripheral pressor action of norepinephrine is potentiated by imipramine, this action may occur at the critical sites in the brain. This would parsimoniously tend to ascribe a rather similar basic mechanism for the two groups of antidepressants, but there is little work that establishes norepinephrine as a central neurohumoral transmitter or as having antidepressant actions on brain. However, it is possible that future work may demonstrate an antidepressant acton of imipramine and/or amitriptyline based upon central adrenergic sensitization.

Another hypothesis for the antidepressant action of amitriptyline and imipramine could be based upon the following facts. Both of these agents exert depressant effects on EEG and behavior in many preparations though they are less powerful than the phenothiazines in this respect. If there are hyperactive neural mechanisms involved in the basis of clinical depression, and anxiety and agitation are present but not readily evident due to the specific form of the symptom pattern adopted by the patients, then the antidepressant action of amitriptyline and imipramine could result from a highly selective depressant effect. This explanation might also be related to the observation that most active monoamine oxidase inhibitors acutely depress behavior and EEG. Devising an experimental test of this hypothesis is certainly a future problem, but there is already suggestive evidence from the clinical reports of the use of a parenteral form of amitriptyline for a selective depressant or tranquilizing effect as the antidepressant mode of action.[46]

Summary

1. The major pharmacological actions of the monoamine oxidase inhibiting drugs have been reviewed and the recent evidence indicates a close link between the block of enzyme activity and the therapeutic actions in man, although not yet a clear causal relationship.

2. The pharmacodynamic actions of amitriptyline, a new antidepressant agent of the non-monoamine oxidase inhibitor class have been described. They include weak tranquilizing and disruptant actions on the EEG and operant behavior, fairly strong anticonvulsant action, weak peripheral atropine-like action, strong antihistaminic property, weak antiserotonin effects, some adrenergic blockade, and a gastric antisecretory effect. The pattern of metabolism was outlined.

3. The actions of amitriptyline and imipramine have been compared and possible modes of action have been suggested.

Amitriptyline was supplied through the courtesy of Dr. E. L. Engelhardt and the preclinical testing was performed in the Merck Institute for Therapeutic Research at West Point, Pennsylvania.

Amitriptyline is available under the trademark Elavil®, chlorpromazine under the trademark Thorazine®, imipramine under the trademark Tofranil®, iproniazid under the trademark Marsilid®, diphenylhydantoin under the trademark Dilantin®, trimethadione under the trademark Tridione®.

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Objective Evaluation of Antidepressant Therapy by Conditional Reflex Technique

LEO ALEXANDER, M.D.*

Certain clinical and physiological observations in patients suffering from depression suggested the interpretation that depression may be a state of inhibition resulting from supramaximal excitation.[1,2] This hypothesis was put to a test by means of the Pavlovian conditional reflex technique as elaborated in Dr. W. Horsley Gantt's laboratory,[3,4] utilizing his method of spacing and alternation of differential stimuli. The stimuli and the responses were recorded continuously on a 5-channel Grass polygraph, as described previously.[5] The results of our study confirmed the hypothesis. It was found[5-8] that the capacity to form conditional reflexes was significantly reduced in patients suffering from depression. The conditional psychogalvanic reflex showed reduction in magnitude and delay as well as impairment of differentiation between the excitatory and inhibitory stimuli, including paradoxical reversal of the responses in that inhibitory stimuli evoked greater responses than excitatory stimuli. (Pavlov's Paradoxical-Ultraparadoxical Phase).

Among a recent series of 40 unselected patients suffering from depression, 32 of whom showed an inhibitory response pattern, were 11 who showed differentiation ratios less than 1; seven of these were paradoxical (differentiation ratios between 0.99 and 0.4; four were ultraparadoxical (differentiation ratios below 0.4); four showed equivalent reactions with equal responses to the inhibitory and the excitatory stimuli. We also found paradoxical reversal of the electrocerebral alerting response in depression, in that hypersynchrony occurred instead of the usual desynchronization.[5] Gluck and Rowland[9] confirmed the interpretation of evoked hypersynchrony as a manifestation of inhibition. By introducing the inhibitory effects of delay and of a differentiated conditional stimulus, they were able to evoke hypersynchronous responses at exactly those phases of the responses at which inhibition was to be expected in the light of Pavlov's findings with the salivary response.

Absence or marked diminution of the positive conditional psychogalvanic reflex, with reduced differentiation between or paradoxical reversal of the responses to the excitatory and inhibitory stimuli, can be considered as an objective positive diagnostic sign of depression, provided the patient is not suffering from organic or toxic disturbance of the nervous system, or from chronic schizophrenia in which similar inhibitory phenomena may be observed.[4,10] By contrast, neurotic anxiety states showed enhanced responses with poor differentiation and other excitatory generalization phenomena. Acute schizophrenic reactions, however, were found to be associated with marked, precise responses with better than average differentiation between excitatory and inhibitory stimuli. While abolition or marked impairment of the positive conditional psychogalvanic reflex constitutes objective confirmation of a diagnosis of depression, preservation of the reflex does not exclude this diagnosis, especially in the case of psychasthenic-anhedonic depressions and in the case of acute situational depressive reactions. In many patients with psychasthenic-anhedonic depression there is a good deal of coexisting anxiety which may preserve or enhance this reflex response. In acute situational depressive reactions, the adaptive capacity of the patient may be unimpaired, hence the preservation of normal capacity for differentiation. Particularly in this clinical area, the test holds promise for usefulness in differential diagnosis, namely, in the distinction between crisis reactions, "people in crisis,"[11,12] as differentiated from actual depressive illnesses. These and other differential diagnostic aspects of the test will be reported elsewhere.

I have found the test clinically useful in the differential diagnosis between depres-

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sive somatization reactions in the form of pain, and physical pain states.[8,10] Patients suffering from psychalgic states incidental to depressive illnesses showed marked inhibition or abolition of the conditional PGR, as is characteristic of depressive states. Spontaneous PGR fluctuations, if present at all, also tended to be minimal. By contrast, patients suffering from physical pain showed marked spontaneous fluctuations of skin resistance corresponding to the waxing and waning of the physical pain, while the responses to the positive conditional stimuli remained uninhibited. Since the state of conditionability appears to be an objective parameter of depressive states, it is of interest to investigate its alteration concomitant with treatment.

Material and Method

The present study is based on 133 depressed patients whose conditional reflex responses were studied before and after administration of antidepressant therapy. Patients treated with electroconvulsive therapy were retested immediately after the completion of the electroshock series, and again at the time when optimal treatment benefits were established, after clearing of treatment-induced confusion, on the average 48 days after the last treatment. Patients treated with drugs were retested one hour after administration of the first test dose of the drug, and/or at the time of establishment of a clear-cut treatment result, either success or failure. In the case of the amine oxidase inhibitors, only the latter retest was used, while for the other drugs both the immediate response and the long-term effect were investigated.

The technique of the test is quite simple. After abolition of the orienting responses, a conditional reflex was established, according to the classical Pavlovian method, by pairing one of two tones with an electric shock to the tip of a finger during the fifth second of the sounding of the tone, while another tone, which was never so reinforced, was presented in regular alternation with the reinforced tone at one-minute intervals. For the purpose of quantitative comparison, only the psychogalvanic responses were utilized because they are easily and accurately measurable, and hence lend themselves readily to quantitative analysis. The well-known inherent difficulties encountered in attempting to analyze the electrocerebral alerting responses by quantitative methods prevented utilization of this portion of our data for this purpose.

Whenever an evoked psychogalvanic reflex response occurred, it was sharply defined and came within about 1.5-2.5 seconds after the beginning of the unconditional stimuli and within 2-3 seconds after the onset of the conditional stimuli. It consisted of an easily distinguishable drop in skin resistance, measured in ohms. Thus, the reaction to the excitatory tone and its overlapping shock stimulus consisted usually of two deflections: the first to the tone, classified as the excitatory or positive conditional response (CR+); the other to the shock, classified as the unconditional response (UR) (Figure 1). The response to the never-reinforced, that is the inhibitory tone, was called the inhibitory conditional response (CR—). In cases of perfect differentiation, such a response was absent and counted as zero. When response to the inhibitory tone occurred, this was usually a response to the on effect, i.e., to the first second of the sounding of the tone, appearing about two seconds after the start

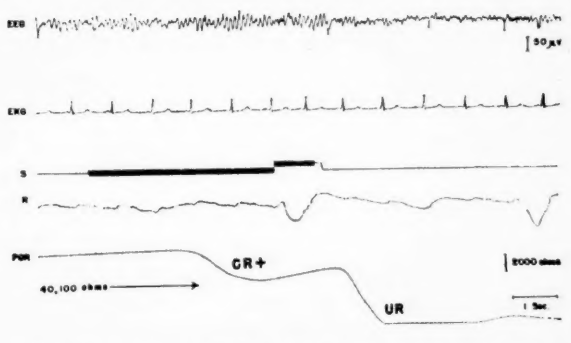

Figure 1. Female, age 27, suffering from schizoaffective disorder. Polygraphic recording illustrating the psychogalvanic reflex responses to the fourth presentation of the excitatory (reinforced) tone and its overlapping shock stimulus. (EEG = electroencephalogram; EKG = electrocardiogram; S = signals (the thick black line denotes the sounding of the tone, the elevation of the base line of the signal channel denotes the shock stimulus to the index finger); R = respiration; PGR = psychogalvanic reflex.) Note conditional PGR response to the excitatory (reinforced) tone (CR+), consisting of a drop in skin resistance of 4000 ohms beginning 2 seconds after the onset of the tone and unconditional PGR response to shock (UR), measuring 7200 ohms, beginning 1.5 seconds after the onset of the shock.

of the sounding of the tone, classified as CR— (Figure 2). This was sometimes followed by an additional response to the fifth second of the tone, occurring about one second after termination of the tone (Figure 3), classified as a generalized time reflex (GTR), since it is obviously a generalization effect by means of a time reflex patterned after the excitatory tone and its overlapping unconditional stimulus.[5]

These four psychogalvanic reflex responses were measured in ohms as the change in skin resistance for each pair of presentations of the tones for all patients before treatment and after treatment. Averages for the responses in each of these four categories were calculated in ohms for each conditioning session which uniformly consisted of 12 pairs of presentations. The bar graphs included in this paper represent the averages computed for each conditioning session. The key to these bar graphs is shown in Figure 4.

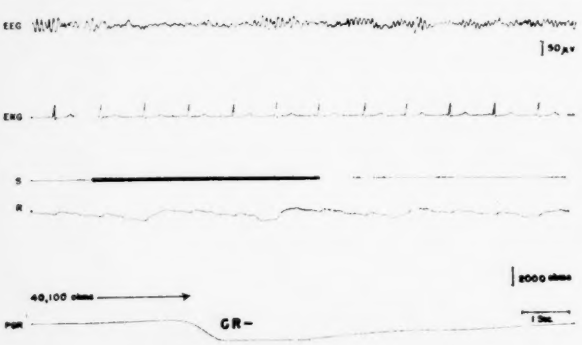

Figure 2. Female, age 27, suffering from schizoaffective disorder. Polygraphic recording illustrating the psychogalvanic reflex response to the fourth presentation of the inhibitory (non-reinforced) tone (CR—) consisting of a drop in skin resistance of 2000 ohms beginning 2 seconds after the onset of the tone.

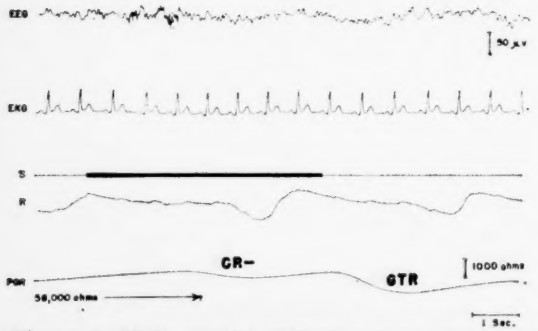

Figure 3. Male, age 24, suffering from psychoneurosis, phobic reaction with obsessive features. Polygraphic recording illustrating a psychogalvanic reflex response to the inhibitory tone (CR—) occurring 2 seconds after the onset of the tone and an additional psychogalvanic reflex response beginning 0.8 seconds after the end of the tone interpreted as a generalized time reflex (GTR) patterned after the response to the excitatory tone and its reinforcing stimulus (compare Fig. 1).

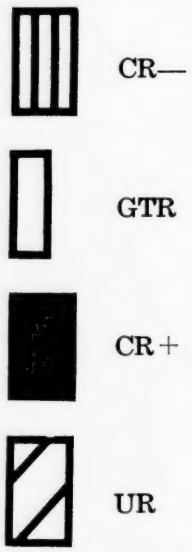

Figure 4. Key to bar graphs shown in subsequent figures.

Effect of Electroconvulsive Treatment

Thirteen patients were studied after electroshock therapy.[7] There were eight psychotic depressions, four neurotic depressions, and one schizoaffective reaction in this group. On pretreatment examination, nine of these showed PGR responses to the excitatory tone which were less than 2000 ohms and hence belonged to the group which we classified as inhibitory types. In two of these nine patients, the response was ultraparadoxical in that the differentiation ratio was less than 0.4, namely, 0.28 and 0.37. All nine patients were suffering from depressive illnesses. There were eight psychotic depressions and one neurotic depression in the group. All of them recovered following treatment, four fully and five socially. When tested three and one-half hours to six days after the last shock treatment, the capacity to form conditional reflexes was completely abolished. Subsequently, enhanced but poorly differentiated activity came to the fore. Ultimately, when retested at the time at which optimal treatment benefits were established after clearing of the treatment-induced confusion (13 to 114 days after the last treatment, the average being 48 days), there was

TABLE I

Electroconvulsive Treatment
Inhibitory Subjects
N = 9

	PGR Averages in Ohms Before ECT	After ECT	One-tail Chi-square Test P
CR—	303	973	.227
CR+	439	1648	.008
Ratio	1.08	2.03	.063
UR	2022	5395	.145
GTR	68	237	.344

a significant increase in the responses to the excitatory signal (Figure 5) from an average of 439 to an average of 1648 ohms (Table I, p = .008). The expected corresponding improvement of the differentiation ratio was suggestive only; it improved from 1.08 to 2.03 (p = .063). This is due to the fact that the responses to the inhibitory signal sometimes increased also, although not to a significant degree (from an average of 303 to an average of 973 ohms, p = .227, Table I). It is of particular interest, however, that the two patients whose responses had been ultraparadoxical before treatment showed a normal type of differentiation after treatment with differentiation ratio values of 1.33 and 2.44 respectively. The increase in positive conditional reflexes associated with a trend toward improvement in differentiation confirms the findings of Gellhorn[13] who showed that electroshock as well as insulin coma may bring about recovery of inhibited conditional reactions. He suggests as a possible reason for this phenomenon that these treatments increase the hypothalamic discharges to the cortex and thus may make subliminal cortical processes supraliminal.

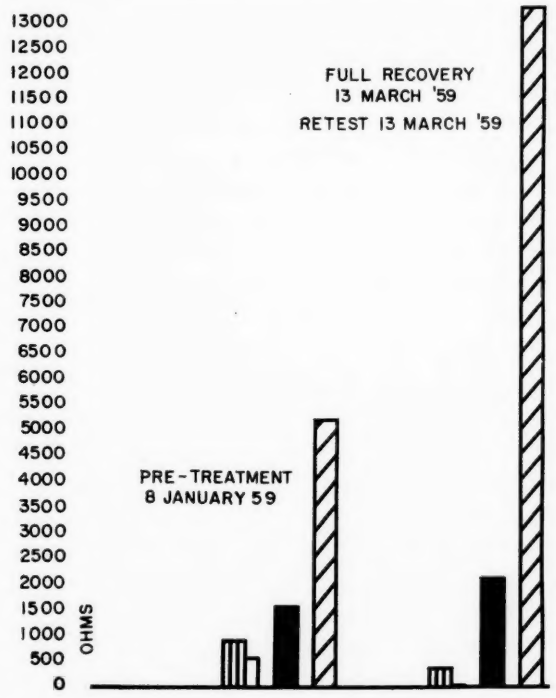

Figure 5. Female, age 53, suffering from depressive reaction, psychotic, agitated, involutional (Issue: anticipated loss). Twenty electroshock treatments were administered between January 12, 1959 and February 23, 1959, resulting in full recovery. The bar graphs illustrate the conditional psychogalvanic reflex pattern before and after successful electroshock therapy. Note increase in psychogalvanic reflex responses to the excitatory conditional stimulus and decrease of those to the inhibitory stimulus, resulting in improved differentiation between responses to excitatory and inhibitory stimulus. The unconditional response was increased also. The generalized time reflex was abolished after electroshock therapy.

The group of patients with pretreatment responses other than inhibitory (N = 4) is yet too small for evaluation. All psychotic depressions in our case material fell into the inhibitory group.

Effect of Meprobamate and Benactyzine in Combination

This test group comprised 39 subjects. Meprobamate and benactyzine in combination improved differentiation markedly, the differentiation ratio (Table II) rising from 3.63 to 12.80 (p = .006). This significant improvement in differentiation was accomplished largely by decrease of the responses to the inhibitory stimuli (p = .046, Table II). There also was a reduction in the generalized time reflex to the inhibitory tone in the majority of the cases. This was significant for the group of subjects with excitatory and average pretreatment test pattern (p = .038), but only suggestive when all cases were included (p = .084, Table II). Changes in the magnitude of the psychogalvanic responses to the excitatory signal were insignificant (p = .872, Table II).

The significant improvement in differentiation characteristic for the effect of meprobamate and benactyzine in combination is, of course, the more impressive the more abnormal responses were prior to treatment. Figure 6 shows the pretreatment and posttreatment responses of the only patient in

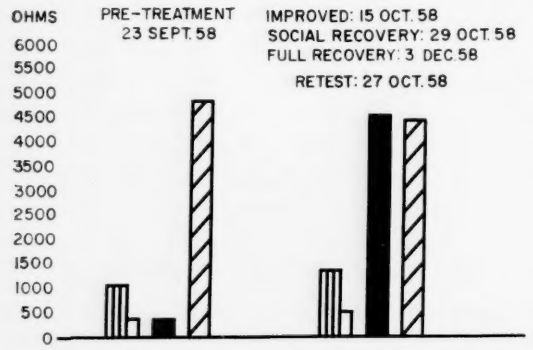

Figure 6. Female, age 67, suffering from depressive reaction, psychasthenic type, psychotic borderline. Treatment with meprobamate-benactyzine combination from September 29, 1958 to December 21, 1958. Dosage 1600 mg. meprobamate and 4 mg. benactyzine q.d., gradually reduced to 400 mg. meprobamate and 1 mg. benactyzine q.d. at time of retest. Note ultraparadoxical pre-treatment test pattern in that responses to the inhibitory stimulus greatly exceed those to the excitatory stimulus. Note change to normal relationship between these responses after five weeks of treatment, concurrent with clinical recovery.

this group whose pretreatment responses were ultraparadoxical (differentiation ratio = 0.34). Five weeks later, following recovery on this medication, the relationship of the responses was normal, the differentiation ratio having risen to 3.31.

Effect of Amine Oxidase Inhibitors

Fifteen patients were tested before and after treatment with amine oxidase inhibitors.[14] Drugs used were iproniazid (eight cases), isocarboxazid, an analogue of iproniazid (three cases), and nialamide (four cases).

The times chosen for the post-treatment retests were those at which emergence of clinical signs of response to the drug appeared, or when treatment failure was established. Only those patients were included in this analysis in whom a clear-cut treatment result was achieved, either success (eleven cases: five, full recovery; six, social recovery) or failure (four cases: two improved short of social recovery; two unimproved). These retest times ranged from 20 to 284 days, the average being 70 days. Earlier retests were carried out from the sixteenth day onward in order to study the timing and gradual evolution of the change in conditional reflex activity, its relation to dosage, duration of its administration and clinical status of the patient. These will be referred to below.

TABLE II

Meprobamate and Benactyzine in Combination

N = 39

	PGR Averages in Ohms		Two-tail Chi-square Test P
	Before Drug	After Drug	
CR—	1272	938	.046
CR+	2925	2783	.872
Ratio	3.63	12.80	.006
UR	6010	4424	.330
GTR	303	186	.084

Marked diminution of psychogalvanic reflex activity was an equally striking feature of the post-treatment pattern in all three subgroups classified by pretreatment test pattern (excitatory, average and inhibitory). Statistical analysis of the changes evident at the time of establishment of a clear-cut treatment result after treatment with amine oxidase inhibitors showed a significant quantitative reduction of responses to the inhibitory and excitatory conditional stimuli ($p = .008$), as well as reduction of the responses to the unconditional stimuli in the majority of the cases ($p = .058$) without significant change in the differentiation between excitatory and inhibitory stimuli ($p = .608$, Table III). There was no significant change of the generalized time reflex. The three different drugs used all contributed equally to these results, the general quantitative reduction in the magnitude of responses being a characteristic of the action of all of them, although they are not entirely equivalent in terms of dosage and time required.

It is of interest that full or social recovery on treatment with amine oxidase inhibitors is consistent with marked reduction in responsiveness of the conditional psychogalvanic reflex, irrespective of whether or not this reflex was already inhibited before treatment. Figure 7 illustrates this further reduction of responses in a patient whose pretreatment test pattern was markedly inhibitory with poor differentiation between the responses to the excitatory and to the inhibitory stimuli. Figure 8 illustrates the reduction of the responses in a patient whose pretreatment test pattern was not inhibitory and whose differentiation between excitatory

TABLE III

Amine Oxidase Inhibitors
(Iproniazid, Isocarboxazid, Nialamide)
N = 15

	PGR Averages in Ohms		Two-tail
	Before Drug	After Drug	Chi-square Test P
CR—	1254	986	.008
CR+	2974	2108	.008
Ratio	4.17	2.07	.608
UR	5126	3484	.058
GTR	293	144	.266

and inhibitory stimuli had been better than average. The post-treatment test, done at the time of consolidation of social recovery (which has remained sustained), shows the conditional psychogalvanic responses practically abolished and the unconditional responses greatly reduced in intensity.

The evolution of the change parallels that of the clinical result, and is related to dosage and to duration of its administration.[14]

While marked diminution of the psychogalvanic reflex response appears closely linked with successful clinical result, a moderate degree of diminution of the reflex may precede clinical improvement in the same manner as the less readily quantifiable increase in tendon reflexes and thus be an indicator that clinical results are obtainable. The therapeutic result may then be accelerated by raising the dosage (Figure 9), or initiated thereby if diminution in conditional psychogalvanic reflex responses had not been forthcoming before. However, the gradual cumulative effect of the drug itself without raising the dosage may be counted upon to bring about improvement in the course of time in less treatment-resistant patients, and this also reflects itself in the psychogalvanic reflex responses. Absence of change of psychogalvanic reflex responsiveness may be a helpful indicator of inadequacy of the initial dosage.

Conversely, when prolonged treatment with an adequate dose of an amine oxidase inhibitor is associated with maximal reduction in psychogalvanic reflex responsiveness, but clinical improvement fails to materialize, it may be taken as an indication that the patient is not likely to improve with continued administration or increase in dosage.

These observations are applicable for testing adequacy of dosage with amine oxidase inhibitors. Such an objectively quantifiable test for the effectiveness of dosage is highly desirable in this group of drugs because of the wide range of effective dosage and the wide range of duration of administration necessary to produce a successful result.[15]

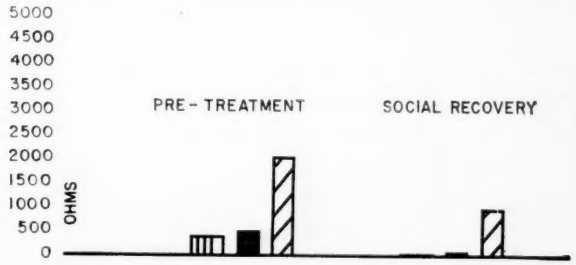

Figure 7. Female, age 46, suffering from depressive reaction with anxiety, neurotic, psychasthenic, chronic (Issue: weakness—envy). Iproniazid treatment January 1958 to June 1958. Note marked reduction of psychogalvanic reflex responses at the time of social recovery on iproniazid therapy. Dosage 150 mg. daily at the time of the retest.

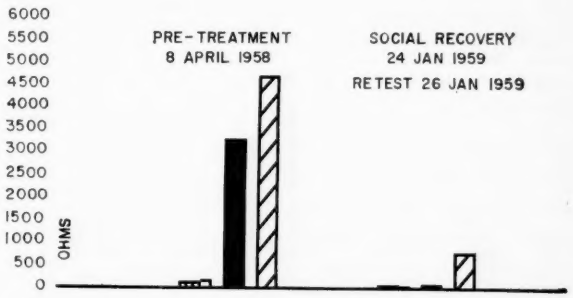

Figure 8. Female, age 64, suffreing from depressive reaction, neurotic, psychasthenic, chronic-recurrent (Issue: weakness—physical inadequacy). Treatment with isocarboxazid November 24th, 1958 to November 18th, 1959. Note marked reduction of psychogalvanic reflex responses two days after social recovery on isocarboxazid. Dosage 20 mg. daily at the time of the retest, 30 mg. daily until two days before the retest.

Effect of Chlorprothixen

This drug brought about a marked reduction in conditional PGR responses to the inhibitory and the excitatory stimuli in all but one of the seven patients studied. Responses to the unconditional stimuli were reduced in five of the seven patients. The differentiation ratio was reduced in six of the seven patients in contrast to the amine oxidase inhibitors where it remained unchanged. The generalized time reflex was reduced in all five patients in whom this response had been

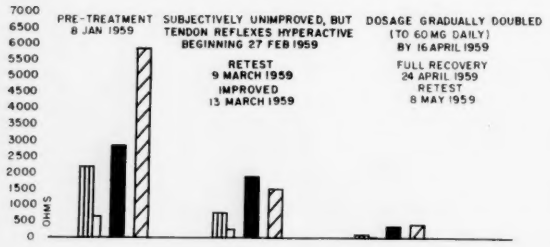

Figure 9. Female, age 76, suffering from depressive reaction, manic-depressive, recurrent, psychotic (Issue: guilt, shame). Treatment with isocarboxazid January 15, 1959 to December 10, 1959. Note moderate reduction of psychogalvanic reflex responses prior to clinical improvement, ten days after tendon reexes became hyperactive, on isocarboxazid, 30 mg. daily. Also note the marked reduction in psychogalvanic reflex responses after full recovery following raising of the dose to 60 mg. daily.

present before. The striking effects of this drug, associated with antidepressant and anxiety-relieving action were, however, in two of the seven patients studied, associated with neurocirculatory side effects which render this drug clinically impractical.

Effect of Imipramine

In the seventeen patients tested with this drug, the response patterns appeared to fall into two distinct groups, dependent upon treatment result. In all but two of the ten patients who failed to respond to this therapy, the post-treatment conditional responses were increased in magnitude. In all but one of the seven patients whose treatment resulted in recovery, the conditional responses decreased in magnitude in the course of treatment. Treatment success was predictable by means of retest one hour after the first test dose of 75 mg. p.o., since in all of the seven patients who recovered on this therapy decrease of the conditional responses manifested itself on that occasion.

The difference between treatment successes and failures with regard to the effect of the drug on conditional psychogalvanic responses may reflect critical levels of dosage requirements. The successfully treated patient (Figure 10) showed a decrease in responses and dedifferentiation after the first test dose of 75 mg. p.o. On this occasion, the differentiation ratio declined from 1.90 to 1.00. On continuous medication of 150 mg. q.d., full recovery supervened seventy days later. When retested at this time, it was seen that the responses had remained low, but the differentiation ratio had improved to 3.69.

By contrast, the unsuccessfully treated patient whose test responses are illustrated in Figure 11 showed an increase in responses, particularly of the GTR (denoting anxiety), without significant change in differentiation ratio (2.94 to 2.69) one hour after the first test dose of 75 mg. p.o. was administered. When treatment had failed, after three and one-half months on a dose of 100 mg. q.d., retest revealed that the responses had increased further (including the generalized time reflex) along with a decline of the differentiation ratio to 1.28 (Figure 11).

In view of the findings emerging from this study, implying that increase of responses combined with dedifferentiation may reflect inadequate dosage, I have recently raised the dosage in the patient illustrated in Figure 11 to 150 mg. q.d. She has since shown signs of improvement (still short of social recovery, however) concurrent with reduction of her galvanic skin responses.

Effect of Amitriptyline

Forty-two patients were studied before and one hour after the administration of amitriptyline, 50 mg. p.o. Seventeen of these patients were also studied after prolonged therapy with this drug. This drug produced a significant reduction in the conditional psychogalvanic responses, with a suggestive increase of the differentiation ratio (Table IV). Decrease of the responses to the inhibitory stimuli and decrease of the generalized time reflex were significant at better than the .01 level of confidence, while decrease of the responses to the excitatory stimuli and to the unconditional stimuli were significant at better than the .05 level of confidence. Increase in the differentiation ratio was suggestive only ($p = .15$, Table IV). The outcome of the one-hour post-drug retest did not differentiate between the 22 patients in this group who recovered, and the 14 who did not recover (the outcome of the remainder is undecided at this time). There was evidence of cumulative effect in that there was further decrease in the responses after prolonged administration. This was significant for the responses to the inhibitory stimuli ($p = .04$). The change in

the differentiation ratio, however, which had been suggestive for the one-hour post-drug retest, became definitely insignificant after prolonged administration when compared to the pre-drug test ($p = .227$). Figure 12 illustrates a typical patient with an inhibitory pretreatment response pattern. One hour after the administration of amitriptyline, 50 mg. p.o., conditional responses were reduced, with improved differentiation, the differentiation ratio rising from 1.28 to 2.77. The unconditional response was likewise reduced. Four days after the achievement of social recovery, forty-eight days after the beginning of therapy, all responses were greatly reduced and the differentiation ratio had returned to 1.0.

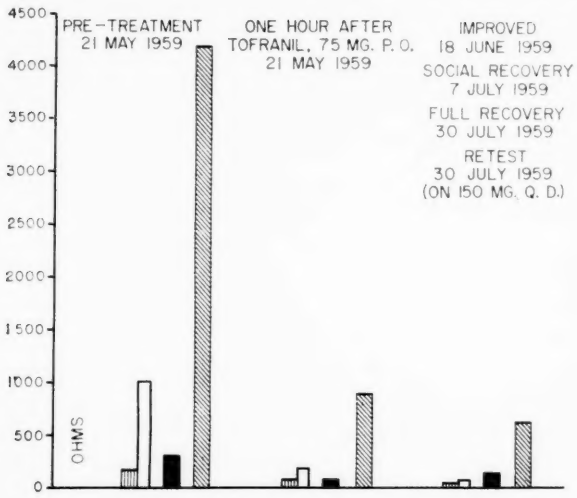

Figure 10. Female, age 57, suffering from depressive reaction, psychotic, involutional, psychasthenic-anhedonie (Issue: loss, weakness, envy). Treatment with imipramine May 21, 1959 to April 11, 1960. Note reduction in psychogalvanic reflex responses one hour after first test dose and after successful treatment with imipramine.

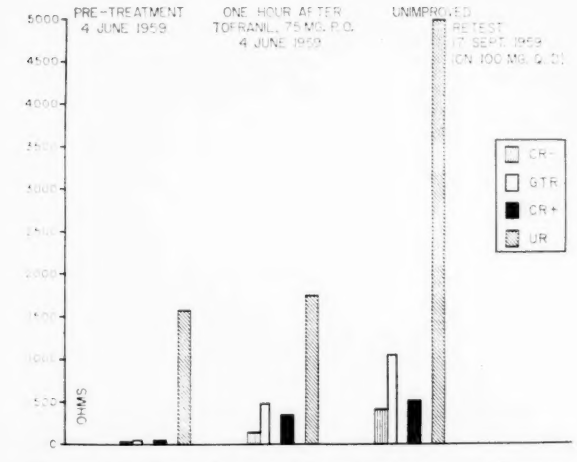

Figure 11. Female, age 38, suffering from depressive reaction, psychotic, manic-depressive type, with hypochondriasis and psychalgia (Issue: Loss). Treatment with imipramine July 20, 1959 to present. Note increase in psychogalvanic reflex responses one hour after first test dose and after treatment failure on imipramine.

Discussion and Summary

None of the drugs studied imitated the 2-phase effect of electroshock therapy which produces extinction of conditional reflex activity during the immediate post-treatment phase, followed during the recovery phase by a consistently significant increase of the positive conditional psychogalvanic reflex, with a trend toward improved differentiation in patients with inhibitory pretreatment response pattern. The drugs either changed the differentiation, or the magnitude of responses, or both. In those drugs which showed a 2-phase pattern of cumulative effect, the initial or mild effect tended to be associated with improved differentiation (disinhibition of differentiation) (see Figures 9, 11, 12), while the late effects were reduced responses without change of or with reduced differentiation. This was the reverse of the sequence observed in electroshock therapy.

Meprobamate and benactyzine in combination improved differentiation largely by decreasing the responses to the inhibitory stimuli. The amine oxidase inhibitors (iproniazid, nialamide and isocarboxazid), as well as a number of other newer antidepressants, namely, chlorprothixen, imipramine, and amitriptyline, brought about marked and consistent decrease of the conditional psychogalvanic responses without significantly altering differentiation between the excitatory and inhibitory signals. While for amitriptyline and chlorprothixen, this decrease in magnitude of responses was general and

TABLE IV

Amitriptyline

N = 42

	PGR Responses After Drug as Compared to Before Drug				
	N Down	N Even	N Up	X^2	P
CR—	31	0	11	9.52	<.01
CR+	28	0	14	4.67	<.05
Ratio	16	0	26	2.38	.15
UR	28	0	14	4.67	<.05
GTR	31	2	9	12.10	<.01

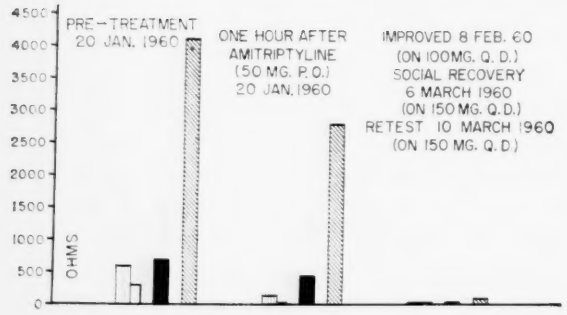

Figure 12. Male, age 49, suffering from depressive reaction, neurotic, psychasthenic-anhedonic (Issue: power). Treatment with amitriptyline January 20, 1960 to March 16, 1960. Note reduction in psychogalvanic reflex responses one hour after first test dose and after successful treatment with amitriptyline.

did not discriminate between treatment successes and treatment failures, for the amine oxidase inhibitors and for imipramine, decrease of the conditional psychogalvanic responses was significantly associated with treatment success, absence of such decrease, or increase, with treatment failure. For the amine oxidase inhibitors, gradual decrease in conditional psychogalvanic reflex responses paralleled the clinical result and was related to dosage and to duration of its administration. This was utilized for testing adequacy of dosage with this group of drugs. A similar approach appears indicated for the regulation of the dosage of imipramine. The fact that amitriptyline brought about a significant reduction of the generalized time reflex (GTR, Table IV), in contrast to the amine oxidase inhibitors (Table III) and the imipramine failures, may be related to the clinical observation that this drug tended rather generally to relieve anxiety in addition to its antidepressant action. It thus appears to occupy an intermediate position between imipramine, which it most closely resembles chemically on the one hand, and chlorpromazine[7] on the other. The mode of action of the inhibiting effect of the newer antidepressants (the amine oxidase inhibitors, imipramine and amitriptyline, on the conditional psychogalvanic reflex is obscure. It may be related to the autonomic effects of these drugs. This is particularly suggestive in the case of imipramine which is known to have a cholinergic effect in low dosage, and an adrenergic effect in large dosage. This fits in quite well with the observation that an ineffective dose increases, while an effective dosage decreases, the conditional psychogalvanic reflex. We cannot be entirely sure whether we are measuring a central effect or a peripheral manifestation of a central effect, but it is conceivable that the drug-induced inhibitory effect upon the conditional psychogalvanic reflex may be obtained by blocking the anterior hypothalamus and releasing the posterior hypothalamus.

The discharges from the anterior hypothalamus to the cortex may thus also be reduced by these drugs, thereby increasing the threshold for certain cortical responses, including those involved in depressive states.

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Iproniazid is available under the trademark Marsilid®, isocarboxazid under the trademark Marplan, nialamide under the trademark Niamid, chlorprothixen under the trademark Taractan, imipramine under the trademark Tofranil®, amitriptyline under the trademark Elavil®, chlorpromazine under the trademark Thorazine®. Deprol® is a combination of meprobamate and benactyzine.

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Effects of an Antidepressant Drug on Tests of Mood and Perception

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I should like to describe our recent work in evaluating the effects of a new antidepressant agent on two newer measures of mood. Our purpose was twofold. We wanted to assay the psychological effects of the drug and, conversely, we wanted to learn more about the utility and reliability of the two methods of mood assessment. The drug used was amitriptyline and the two psychological tests were the Clyde Mood Scale and the Apparent Horizon Test.

Amitriptyline has been employed as an antidepressant because of its close structural resemblance to imipramine and the similarity of their effects in animal behavior studies. Dorfman,[1] Barsa and Saunders,[2] and Ayd[3] treated 40, 28, and 130 patients respectively with amitriptyline. Most of these patients were hospitalized depressed schizophrenics, involutional melancholics or in the depressed phase of a manic-depressive psychosis. The agent was administered by mouth in doses of 25 to 75 mg. three times a day. Improvement, when it occurred, was noted within the first month of treatment. Side effects were not prominent and usually consisted of dry mouth, blurred vision, and giddiness.

The Clyde Mood Scale is an adjective check list.[4] Its 133 items were selected after studying other psychiatric rating scales and clinical reports of the effects of tranquilizers and stimulating drugs. Clyde recommends scoring the scales for six intercorrelated factors. These factors or scales were arbitrarily named "Friendly," "Energetic," Clear-thinking," "Aggressive," "Jittery," and "Depressed." The "Depressed" scale, with which we shall be principally concerned, has 59 items. The key items are "depressed," "troubled," "downhearted," and "unhappy." This Mood Scale has been employed by us in assessing effects on mood of LSD, JB 318 and atropine.[5,6]

The term, "apparent horizon," when used here means the estimated eye level under standard conditions. There is a kind of inherent validity to the notion that when a man is elated, he feels taller. His head is held high, his horizon elevated. Conversely, when downhearted, he is smaller, "hunched up" and his horizon lower. Rosenblatt[7] and Wapner, et al.[8] showed that disorders of affect, either occurring in life or induced in the laboratory, were associated with changes in the perception of the apparent horizon. Krus presented some evidence that affective changes produced by psychotropic drugs also altered the perception of the apparent horizon.[9] He demonstrated that iproniazid caused subjects to overestimate the apparent horizon and reserpine to underestimate it.

The apparent horizon apparatus consists of a lightproof box with a face of frosted glass. Across the middle of this face is a horizontal black line. The glass face is illuminated from within by a small light bulb. The box is attached to a stand and can be moved up and down. The task evaluates the individual's ability to estimate the distance of his eyes above the floor. The subject, wearing opaque goggles, is placed in a standard chair with his head loosely confined in a halter-like arrangement. The distance of his eyes above the floor is measured. The black line is then set at the level of the subject's eyes and the room is darkened. Upon removing the goggles, the subject sees the black line. His task is to direct the experimenter to move the line so that it is even with his (the subject's) eyes. The task consists of three such trials with the goggles being returned to the subject's eyes between each trial. The final score is the mean of the three trial scores.

Method

Three sets of experiments were carried out. In all experiments, the subjects were unaware of the identity of the drug or its possible effects. In Experiment 1, the subjects were ten male medical student aged 21 to 27 who were veteran participants in drug experiments. All were free of bodily illness and were functioning well psychologically in

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a medical school environment. Each subject reported to the laboratory in the morning in a post-absorptive state. He completed a Clyde Mood Scale, and the Apparent Horizon task was administered. Then 50 mg. of amitriptyline was taken by mouth. In one hour both behavioral measures were repeated. This experimental design did not make allowance for the effects of order on the two tests. However, concern about day-to-day fluctuations in mood and their possible influence on the tests prompted us to do all testing within as short a time as possible.

Experiment 2 was aimed at learning more about the relatively long-term effects of these agents on mood. Six male medical students and physicians aged 21 to 33 were subjects. In three, the "control" Mood Scale and Apparent Horizon task were administered before the drug period, and in three a few days after the drug period was completed. This was done to eliminate order effects. Each drug test was administered during the fourth week of a one month period on the drug. The dose was 25 mg. three times daily.

In Experiment 3, sixteen patients with neurotic depressions were subjects. None of them were hospitalized or socially grossly incapacitated; 11 were women, five men. Age range was 26 to 56 and all were Caucasian.

In counterbalanced order these subjects received placebo for one month and amitriptyline for one month. The dose was 50 mg. four times daily. The Clyde Mood Scale and Apparent Horizon task were administered during the last week of the placebo period and during the last week of the drug period. Each subject was also questioned on these occasions about symptoms and general feeling state. The Wilcoxon matched-pairs signed-ranks test was used for the mood scale and paired T test for Apparent Horizon task in determining significance of differences.

Results

The volunteers in Experiment 1 exhibited a significant increase in the estimation of the apparent horizon during the drug period as compared to their predrug estimates ($p<.01$). The mean increase was 2.4 cm. None of the scales of the Clyde Mood Scale showed significant changes although in six of the ten subjects the "Depressed" scale showed a decrease (Table I). They did not report any changes in mood or thought.

The subjects of Experiment 2 exhibited a rise in the estimated horizon which averaged 1.6 cm. The Clyde Mood Scale also showed some changes. The "Energetic" scale score was decreased in four of the six subjects during the drug period. The "Depressed" scale showed no consistent change, being lower in three subjects, essentially unchanged in two and higher in one. Because of the small number involved, no tests of significance were done.

Twelve of the 16 subjects in Experiment 3 stated that they felt better during the drug period as compared to the placebo period. By feeling better, they meant an improved feeling state, more optimism, and some increase in energy and interest in surroundings and other persons. Two indicated that they felt better during the placebo period and two could see no difference between the drug and placebo periods. There was a significant increase in the estimated height of the Apparent Horizon ($p<.01$). The mean increase for the group was 2.1 cm. Similarly, the "Depressed" scale scores fell significantly. Changes in the other scale scores were minor and not significant.

TABLE I

	Acute Experiment Volunteers		Chronic Experiment Volunteers		Chronic Experiment Patients	
Scales	Predrug	Postdrug	Predrug	Postdrug	Predrug	Postdrug
Friendly	43.3±9.12	42.6±8.23	41.5±7.03	43.2±6.31	38.-± 8.02	40.4±7.12
Energetic	48.1±8.79	46.2±7.71	50.2±6.55	47.6±7.08	44.2± 8.71	45.8±6.65
Clear-thinking	45.2±5.88	43.6±4.95	48.1±5.21	47.0±5.93	46.0± 7.36	44.8±6.32
Aggressive	52.6±6.73	51.0±6.32	50.2±4.38	48.7±5.01	47.3±10.18	46.0±5.19
Jittery	45.3±4.54	43.6±5.03	43.8±5.83	45.0±5.12	48.7± 8.13	46.2±7.41
Depressed	46.0±7.31	43.7±6.22	47.2±7.62	45.1±6.37	57.4± 9.06	48.2±6.37

The scores are standardized.

In none of the subjects who took the agent for a month were there any notable side effects. None had to discontinue taking the drug because of untoward symptoms. Dryness of the mouth and slight giddiness were reported by two subjects.

An attempt was made to see if there was a significant relationship between mood scale score changes and changes in the apparent horizon. The subjects in Experiment 3 were ranked from 1 to 16 by magnitude of the drug-induced decreases in the "Depressed" scale scores. They were then ranked from 1 to 16 by the magnitude of rises in the estimation of the apparent horizon. A rank order correlation coefficient between the two variables was determined. This correlation coefficient equalled .61 and was positive in algebraic sign. A significant and positive association between the two drug-induced changes was demonstrated ($p = .01$).

Discussion

A close parallel between reported general improvement in feeling state, "Depressed" scale score lowering and increases in the height of the apparent horizon was demonstrated. Both of the quantitative tests appeared to provide a reliable and semi-objective means of assessing the drug-induced symptomatic improvement in these patients. Their use in studies of other antidepressant or antianxiety agents seems warranted.

One difference in results between the patient group in Experiment 3 and the non-patient group in Experiment 2 was apparent. In the patients, the "Depressed" scale was significantly decreased by the drug and in the volunteers there was essentially no change.

The "placebo" "Depressed" scale scores of the patient group were distinctly higher than the control scores of the non-patient group on the same scale. There were, of course, many other differences between the two groups besides this one. It is not surprising that a drug should have an effect on mood in subjects with a pathological disturbance of mood and no effect on a normal group. Many drugs have different effects on ill and well patients. Digitalis has little effect on a normal heart in doses that will greatly help a failing heart. Ganglionic blocking agents lower blood pressure in the hypertensive patient in doses which have much less effect on normal blood pressure. Clearly, the state of the patient at the time the drug is given is an important determinant of the effect.

Finally, it appears that amitriptyline in the doses employed here is relatively effective in depressed states of neurotic proportions. Its freedom from severe side effects in doses that are therapeutically effective seems established in this patient population.

One final word. This work is not meant to suggest that human feeling states can be assessed in centimeters or psychiatric diagnoses made by adjective check lists. Only two simple assumptions underlie these tests: 1) that perception is modified by mood, and 2) that persons are aware of changes in the intensity of their moods and can report these changes.

Amitriptyline is available under the trademark Elavil.®

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Psychotherapy and Chemotherapy (Amitriptyline) of Anergic States

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The title of this paper may be suggestive of a dichotomy between psychotherapy and chemotherapy in the treatment of some psychiatric states. This is not my intent; to the contrary, one type of approach is essential to the success of the other and without integration of both modalities into a common therapeutic program, either or both forms of therapy may be doomed to failure.

I refer to anergic states rather than to depressions *per se,* because in my experience there are some types of schizophrenia whose symptomatology is such that they more properly classify for treatment with antidepressant drugs than they do into a regime where the chemotherapeutic efforts are best suited for the amelioration of hypersymptomatology. Certain types of schizophrenia, particularly the withdrawn, inactive, seclusive, regressed, apathetic, morbidly preoccupied, disinterested and even depressed schizophrenics not only seem to respond favorably to the psychic energizer type of compound, but respond adversely—as do many depressions—to tranquilizer medication.

I do not mean to imply that, because certain types of schizophrenia seem to respond to antidepressant medication, their fundamental psychopathology is similar to that of true depression. Such a rationalization is unnecessary, just as it might be for presuming a common psychopathology for the manic-manic and the excited schizophrenic, though both respond well to tranquilizer therapy. Many of us in the '40's and early '50's did administer electroconvulsive therapy to both the hyperactive schizophrenic and the manic-manic without too much concern over the fact that these two states did not share a common psychopathology.

Psychodynamically, depression is viewed as an internalization of hostile impulses with resultant feelings of guilt, depression, etc. Freud classically emphasized three factors in the psychodynamics of depression: (1) The loss of a love object, whether it be a person, an ideal, money, etc.; (2) A personality structure characterized by emotional ambivalence towards one's own ego (with elements of hostility vying with elements of self-love) and with the hostile elements being demonstrated in the depression, and (3) withdrawal of the libido and introjection within the individual hmself.

The depressive syndrome is of such a nature that it is conducive of an emotional setting wherein the individual may atone by suffering and eventually be restored to health. For this reason, our psychotherapeutic regime—the antidepressive regime—is so structured as to implement this need for suffering and atonement.

Many clinicians and writers have pointed out as the cardinal features of the depression such symptoms as psychomotor retardation, apprehension, negativism, inertia, decreased sexual desire, hallucinations, delusions, hypochondriasis, weight loss, etc. Obvicusly such symptomatology is not the exclusive prerogative of the cyclothymic personality.

I had the good fortune to attend the McGill Conference on Depression in Montreal a year or so ago and perhaps my outstanding recollection of that meeting was the inability of an international congress of experts to agree as to what symptomatology is pathognomonic of depression.

From a psychotherapeutic standpoint, the depressions and the anergic schizophrenics present a common challenge—their inaccessibility to psychotherapeutic overtures. This, to some extent, accounts for the enthusiastic reception accorded to the somatic modalities in the treatment of these states. The use of electroconvulsive therapy, insulin coma therapy, or one of the other somatic modalities does not make mandatory for their success, the active participation of the patient, and these modalities were thus suited for use in the treatment of the withdrawn, apathetic, disinterested, inaccessible, negativistic patient.

When the somatic modality had produced a therapeutic effect and promoted a change

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in the patient in the direction of increased coparticipation, accessibility, interest in environment, etc., we could then add to the regime the potentialities of a well-planned and integrated psychotherapeutic program.

Electroconvulsive therapy and insulin coma therapy served their purpose well and they are now being supplanted only because we have been provided with other modalities —chemotherapeutic ones—for inducing reactivation of the patient.

Despite claims for specificity, I question whether our new psychotropic agents, whether they be tranquilizer or energizer, have real specificity insofar as their effect on the basic underlying psychopathology is concerned. Rather, irrespective of the underlying psychopathology, these drugs appear capable of altering or ameliorating certain symptoms.

Our experience has been that the tranquilizers can ameliorate over-activity, whether it be generated by a schizophrenic or manic process. In a similar sense, the energizers appear to be potent in re-endowing anergic individuals, stemming from a depressive or a schizophrenic process.

That the psychic energizers have been effective in the treatment of depression is well attested to in the current literature. Not as commonly recognized or accepted, however, is that these same drugs are also effective in the treatment of certain schizophrenic states. To many of the schizophrenics, their detachment from their environment is of such a malignant degree that they are inapproachable psychotherapeutically. It is in the re-establishment of this very basic attachment to the environment that the energizer compounds appear to have merit.

Some critics of this concept have argued that those schizophrenics who do respond to energizers may have been improperly diagnosed or had "a depressive overlay." Such arguments, however, pay lip service to the concept that these drugs act upon the underlying process and have specificity in this respect. It is incontestable, however, that not only the depressions but some types of schizophrenia as well show desirable changes following use of energizers.

Most noteworthy in the response of the anergic schizophrenic to energizer therapy has been an elevation of mood, renewed interest in the environment, increased availability of energy for interacting with the environment and, as a consequence of all of this, the conversion of the patient to a state wherein psychotherapy in its varied forms becomes feasible.

One of the important developments in the current era of chemotherapy has been a clarification of the great importance of the various parameters of therapy. Psychosocial, personal, clinical, therapeutic and other factors in the total milieu are receiving more and more attention. Today it would be considered naive to presume that the simple administration of a drug, without its integration into a total treatment program, would be very effective.

That we are meeting with success in the use of the new chemotherapeutic agents, and perhaps a superior form of success, is evident from the gradual but definite abandonment of electroconvulsive therapy and insulin coma therapy. This is at present a nationwide phenomena. At the Topeka State Hospital, which has a 1,000 patient census, we have maintained accurate and complete records on the use of all therapeutic modalities. Figure 1 depicts the fate of the two major somatic modalities and its relationship to the introduction of the psychopharmacotherapeutic agents.

The initial drop in the incidence of use of electroconvulsive therapy and insulin coma therapy coincides with the introduction of the tranquilizers. The decrement of the insulin curve is continuous and progressive. The final abandonment of this form of therapy appears more precipitous than it might

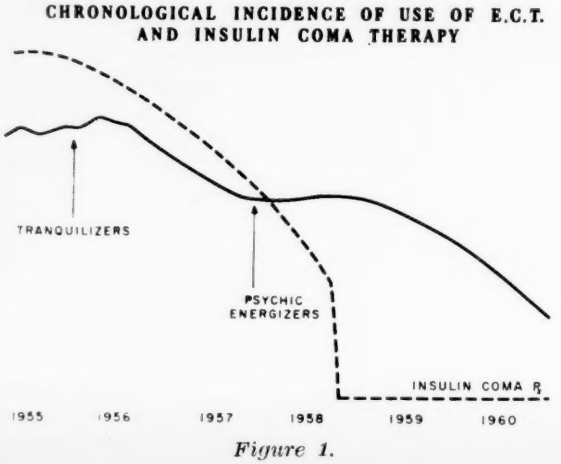

Figure 1.

have been and was prompted by an administrative directive.

The electroconvulsive therapy curve, after an initial drop coinciding with the introduction of the tranquilizers, reached a plateau which was then maintained because of its continued (but curtailed) use in some schizophrenics and in the depressions. A second drop ensued when the psychic energizers were introduced. I am not predicting as yet a complete abandonment of electroshock, but certainly a drastic curtailment of its use has already occurred and appears to be in the process of continuing.

The developments in the field of antidepressive pharmacology are reminiscent of those that occurred just a few years ago with phenothiazine tranquilizers in that, in both instances, a number of analogs were developed. In the case of the antidepressants, the hydrazine analogs of iproniazid displayed distinct activity of a desirable nature, and sometimes degree, but this was marred at times by excessive toxicity.

The development of imipramine was a major break-through in antidepressive pharmacology and this compound had fewer of the undesirable features of the hydrazine compounds. I consider it a superior antidepressant but of late we have witnessed a peculiar, toxic incompatibility between it and the monoamine oxidase inhibitors.

My interest in amitriptyline stemmed from the fact that it represented a further manipulation of the phenothiazine ring in a direction similar to that utilized in developing imipramine (Fig. 2). In addition to the double carbon substitution for the sulphur, amitriptyline has a carbon substitution for the nitrogen.

We have to date tested amitriptyline in 195 patients, all of whom were screened to eliminate hypersymptom patients from this study report. Without exception, each of the patients in the study received amitriptyline as only one part of a total treatment program. In those instances where patient-response made it feasible, the psychotherapeutic program was enlarged in keeping with the patients' needs and capabilities.

The test group is almost equally divided by sex. The schizophrenic group (112 patients) had an average age of 33 years and an average chronicity of illness of 10 years. The depressed group (83 patients) had an average age of 41 years and an average chronicity of illness of one year.

The total group was treated for an average of 97 days with amitriptyline. Before, during and after the course of chemotherapy, a complete battery of laboratory tests were performed. These included renal, hepatic and hemopoietic profiles.

A variety of maximum dosage levels were used. Figure 3 indicates that, in this study, greatest therapeutic efficacy was obtained at dosages between 150-200 mg./day. Responses at dosages of 225-250 mg./day also appear to be effective, but do not seem to possess any advantage over the lesser dosages.

The entire test group, consisting of both true depressions and anergic schizophrenics, showed significant improvement in 53% of the trials. By diagnostic categories, 46% of the schizophrenics and 72% of the depressives showed a favorable response.

Table 1 indicates the changes in the specific criteria of evaluation upon which overall improvement is based. These criteria are

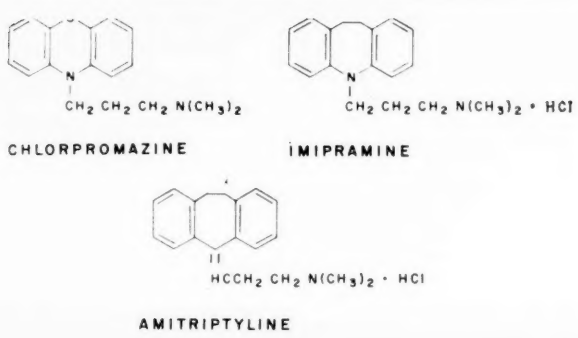

Figure 2.

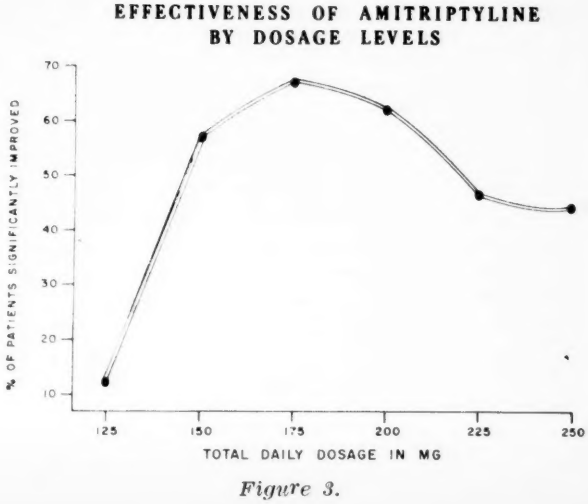

Figure 3.

listed in an order of diminishing efficacy of response to amitriptyline. Quite clearly, the results suggest that amitriptyline has an energizer profile, and in keeping with this is quite effective in producing desirable changes in such symptomatology as anergia, tension, interest in environment, etc. Like other antidepressant drugs, the response of delusions and hallucinations, etc., to amitriptyline is disappointing.

Compared to other energizer compounds, particularly the hydrazines, amitriptyline appears to be relatively nontoxic. The laboratory reports for the most part remained within normal limits. Occasionally, abnormal readings were reported, but these appeared only sporadically and were not related to any clinical findings.

Table 2 indicates the incidence and type of side effects. Occasionally, exacerbation of hallucinations and delusions occurred, but responded well to the incorporation of a phenothiazine into the treatment regime. The tendency for depression to swing over to the hypomanic or manic side was infrequent, occurring in but three patients, and again a phenothiazine was effective.

Many patients in the test group had been treated with other antidepressant drugs prior to trial with amitriptyline. From data based upon patients serving as their own controls, Table 3 indicates that amitriptyline seems to be on a par with imipramine, slightly more effective than nialamide and iproniazid, and definitely more effective than phenylhydrazine, chlordiazepoxide and benzylhydrazine.

With the development of amitriptyline we have a drug which appears to be effective in the treatment of depressive and anergic states. In the project upon which this paper is based, the chemotherapeutic agent (amitriptyline) is but one facet of a total treatment program which was structured to mobilize all possible therapeutic modalities in a concerted effort to rehabilitate the patients. In such a setting, the results that were obtained were most gratifying.

TABLE 1

Response on Individual Target Symptoms to Amitriptyline

Target	% Sig. Impr.
Participation in Adj. Therapy	68
Tension	67
Hypo-activity	62
Appetite	58
Interest in Environment	56
Sleep	51
Dress and Personal Hygiene	49
Amicability	42
Affect	42
Accessibility	40
Appropriateness of Conversation	31
Bizarre Mannerisms	18
Delusions	18
Hallucinations	14
Negativism	13

TABLE 2

Side Effects Due to Amitriptyline

(195 Patients)

Symptom	Incidence
Blurred vision	7.1%
Dizziness	6.7%
Dryness of mouth	4.1%
Nausea	3.6%
Emesis	2.6%
Nasal stuffiness	2.6%
Rash	2.1%

TABLE 3

Comparative Efficacy of Drugs

	Amitriptyline (Elavil)		
Other Drug	On a Par	Sl. Sup.	Sig. more Sup.
Imipramine	×		
Nialamide		×	
Iproniazid		×	
Phenylhydrazine			×
Chlordiazepoxide			×
Benylhydrazine			×

Drugs referred to in this paper are available under trademarks as follows: amitriptyline as Elavil®; imipramine as Tofranil®; nialamide as Niamid; iproniazid as Marsilid®; phenylhydrazine as Nardil; chlordiazepoxide as Librium®; and benylhydrazine as Marplan®.

DISCUSSION OF PAPER BY DR. FELDMAN

LOUIS LINN, M.D.
New York, N. Y.

Dr. Feldman is a pioneer who has tried to integrate a knowledge of the newer psychotropic drugs with a knowledge of psychodynamics. His paper is an excellent example of highly skilled interdisciplinary psychiatric research. The data presented promise an important addition to our armamentarium of antidepressant drugs.

First of all, Dr. Feldman has touched upon the important problem of nosology. It is becoming increasingly clear, as Dr. Holt's summary confirms, that depression is comparable to anxiety in the sense that it is a symptom complex that can occur in any diagnostic category from normal mourning to depressive reactions in schizophrenia. Without exception depression is always part of a larger symptom complex and treatment of the depression cannot be divorced from treatment of the major psychiatric illness of which it is a part.

Dr. Feldman has reminded us of Freud's thesis that the normal mourning process is the model and the clue to psychological understanding of depression. The crux of the melancholic's problem, in Freud's view, is that he has suffered a loss of some vitally important source of self-esteem. For those who insist that there is an irreconcilable conflict between the psychoanalytic and the psychopharmacologic approach to depression, it may come as a surprise to learn that Freud, writing in 1917, hypothesized that the deep sense of loss, "the impoverishment of the ego libido," characteristic of depression, is in some instances due directly to toxins, and that, in these cases, successful treatment will depend on the use of chemical agents to neutralize the effects of these hypothetical toxins.

The term "anergic states" calls to mind that depressive reactions, like the schizophrenic syndrome, can be viewed as taking place in two stages. There is an initial period of trauma with simple depression. In response to the psychological trauma, the individual withdraws his interest, or his libido, from the world about him which manifests itself clinically as an "anergic state."

The second stage represents the first steps forward recovery. The traumatized patient strives to contact the world again. In depression this may manifest itself by agitation, just as in schizophrenic reactions it may express itself in florid delusions and hallucinations. The so-called "psychic energizers" tend to drive the individual in the direction of recontacting the world.

And now a word about the term "psychic energizer." I would like to echo the serious doubts of previous speakers concerning the propriety of the term "psychic energizer." I have long been impressed that a variety of agents acting diffusely on the brain and producing an impairment of general awareness can facilitate certain psychological mechanisms of defense, notably denial and repression. A consequence of such changes is the appearance of elation where a state of depression existed before. Many of the so-called energizers are actually toxic substances, and the "paradox" referred to by Dr. Klerman is a really familiar phenomenon. Experimental data can be cited to substantiate the fact that the antidepressant action of these drugs often parallels their toxic action. Dr. Vernier's data today is in line with this point of view. In any event, many so-called "energizers" are at best "pseudo-energizers," and in experimenting with new drugs we can never relax our vigilance over the cerebral toxic component in so many of them.

I have been impressed with a certain group of cases, schizophrenic patients with depressive reactions in whom a suicidal drive is associated with fixed delusions. For them, suicidal behavior is not, as in other depressive reactions, an essentially rational plea for help, but rather a direct attempt at problem solving in psychotic terms. These patients are singularly unresponsive to psychotherapy. Antidepressant medication works too slowly, and in any event, often intensifies the delusional system. For these cases, prompt and intensive EST seems to remain the treatment of choice.

How effective are these drugs in the hands of the general practitioner? In my mind, not as effective as in the hands of the psychiatrist. First because the general practitioner gives the drugs in ineffective doses. Second and perhaps more important, the depressed patient has need of skillful psychotherapy. Initially, the depressed patient needs emotional supportive help. As he improves, he must be helped to recognize the hostility which he has turned inward upon himself, and encouraged to direct it outward. Finally, the patient must be helped to cope with any family turmoil resulting from his improvement.

A Critique of Antidepressants

FRANK J. AYD, JR., M.D.*

In the spring of 1957, the euphoric effects of iproniazid were rediscovered and successfully employed in the treatment of melancholia. As a consequence, the attention of psychiatrists was diverted from schizophrenia and focused on the depressive illnesses. Simultaneously, the pharmaceutical industry launched an aggressive search for more antidepressant compounds. Since the mood-elevating properties of iproniazid were ascribed to its inhibition of brain monoamine oxidase, similar enzyme inhibitors were tested and found to be antidepressants. Within two years, four additional amine oxidase inhibitors, pheniprazine, isocarboxazid, phenelzine, and nialamide, were introduced. Meanwhile, the fortuitous observation that a non-amine oxidase inhibitor was an antidepressant added imipramine to the expanding list of chemical remedies for depression. It also sparked the study of other compounds which structurally and pharmacologically resembled imipramine. This led to the development of amitriptyline.

Concomitantly with this pursuit of new pharmaceuticals for melancholia, there have been in the past four years more scientific meetings, more publications, and more discussions on the nature of affective disturbances and their causes, recognition, and treatment than ever before. In view of the extent of the interest in and the clinical experience with these drugs, a critical evaluation of them seems appropriate. Are these compounds true advances in the treatment of depression? Are they superior to the older, tried, and proven electroconvulsive therapy? Are they the long-desired and sought for solution to the problem of prevention of recurrent melancholic states? It is extremely difficult to answer these important questions by an appraisement of the reports on these drugs because some are overenthusiastic, premature, uncritical, and unscientific, made after a brief clinical trial while others are hypercritical reviews based on insufficient evidence. A comparison of the opinions held and the results obtained by psychiatrists is confounded by the fact that diagnostic criteria vary, dissimilar treatment methods are used, and standards of recovery are differently assessed. Therefore, this critique is based primarily on my own experience with antidepressants.

During the past five years as an investigator and therapist, I have studied the human pharmacology of, and clinically evaluated under carefully controlled conditions, a galaxy of antidepressants. These trials were undertaken to ascertain if the agent is safe and effective when prescribed for a multiplicity of patients with their myriad idiosyncrasies. The majority of these drugs was soon found to be unsuitable for use because they were either unsafe or ineffective. The experience gained from testing these compounds made it possible, however, to be more astute in the screening of other antidepressants to determine their differential effects.

It has become fashionable in some psychiatric quarters to censure clinical investigators for their failure to employ control groups, placebos, double-blind techniques, or adequately designed studies. This pedanticism emanates from sophists who seldom have had extensive experience in the art of drug evaluation, who are equally as guilty of making unwarranted generalizations as those they criticize, and whose expensive, time-consuming and personnel-involved experimental designs months or years later are contradictory or merely verify, in most instances, the original findings of the careful, experienced clinician. Statistics and double-blind studies, although impressive, have their pitfalls and are of limited significance when it comes to choosing the individual patient for treatment with these drugs. These observations in defense of the competent clinical investigator are necessary because this critique is founded on studies which lack control groups, placebos, and double-blind techniques.

The initial reports by Kline and his associates[1] and by Crane[2] at the American Psychiatric Association Regional Research Conference in Syracuse, New York, in April, 1957, heralded iproniazid as a new "psychic

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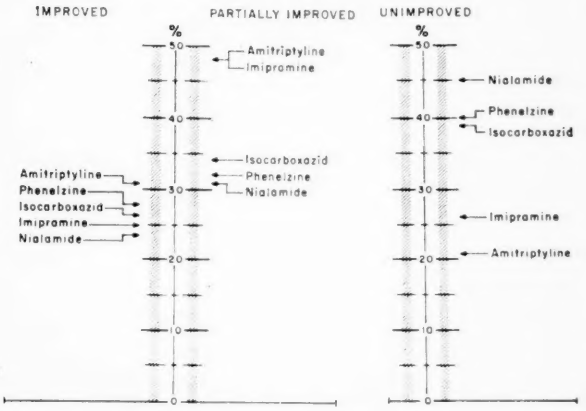
energizer" which elevated mood, stimulated appetite, increased weight, and restored vitality. As a result, this drug was recommended for the treatment of depression and debilitation. In "A Preliminary Report on Marsilid" published in the November 1957 issue of the *American Journal of Psychiatry,* I wrote that half of the fifty patients started on iproniazid did not benefit from this drug, that it is not always a psychic energizer, that it may be a tranquilizer or a psychotomimetic drug, and that, although potentially useful, it should be prescribed cautiously for patients who can be supervised carefully.[3] A subsequent report on a larger group of patients treated with iproniazid over a longer period of time was published in January 1958.[4] In this article, I re-emphasized the therapeutic limitations of this drug and called attention to its undesirable side effects. However, with any new drug it is not possible to know all its potential dangers until it has been prescribed for a multitude of people. Thus, months passed before the hepatotoxic properties of iproniazid were uncovered. In the meantime, another amine oxidase inhibitor, pheniprazine, although endowed with antidepressant effects, also was limited in its therapeutic application by unpleasant and potentially serious side effects. A short time later pheniprazine also was discovered to be hepatotoxic. Because prolonged use yielded the hazardous side reactions of these drugs they have been withdrawn and are now obsolete. For this reason iproniazid and pheniprazine are not included with the antidepressants to be discussed.

Time limitations do not permit a detailed description of the experimental design employed in the screening of amitriptyline, imipramine, isocarboxazid, phenelzine and nialamide. Suffice it to say that for each drug studied, the patients were matched as closely as possible according to age, sex, diagnosis, severity and duration of illness, and prognosis. The selection of cases was based on the same target symptoms. One hundred patients were treated with each antidepressant except amitriptyline, which was administered to 130 depressives. All these drugs have been studied for at least 14 months.

The starting dose for each drug was based on the clinical estimate of the severity of the target symptoms; subsequent dosage was increased or decreased, depending on the clinical response and tolerance of the individual patient. The initial daily dosage was: amitriptyline, 100-150 mg.; imipramine, 100-150 mg.; isocarboxazid, 30-60 mg.; phenelzine, 45-60 mg.; and nialamide, 100-150 mg. Similar techniques of therapy were utilized for each drug, and the same criteria for improvement were used. A comparison of the therapeutic results with these various antidepressants is listed in Table I.

TABLE I

Comparison of Therapeutic Results with Various Antidepressants



Daily dosage:
Amitriptyline 100-150 mg. per day (130 patients).
Phenelzine 40-60 mg. per day (100 patients).
Isocarboxazid 30-60 mg. per day (100 patients).
Imipramine 100-150 mg. per day (100 patients).
Nialamide 100-150 mg. per day (100 patients).

Although each drug exerted its beneficial effects within a month, there was a difference in the speed of action. Some patients began to improve as early as the third treatment day, but as a rule, amitriptyline and imipramine were the fastest acting, their therapeutic effects becoming evident in 4 to 10 days; isocarboxazid and phenelzine required 10 to 20 days to produce their effects; and nialamide was the slowest acting, its favorable action appearing in 14 to 21 days.

For each drug there was a correlation between the total daily dosage and therapeutic results. To achieve improvement with imipramine and amitriptyline, a minimum of 75 mg. a day was necessary. The most effective daily dosage of these drugs was 150 mg. a day. A significant number of patients required 40, 60, or 90 mg. a day of isocarboxazid to achieve therapeutic benefit. The

most effective daily dose of phenelzine was 45 mg., although occasional patients needed 60 mg. or more a day to attain improvement. The daily dosage-therapeutic result relationship for nialamide was 100 mg. a day minimum and 200 mg. maximum, the most effective daily dose being 150 mg.

Since these drugs were administered to control or eradicate target symptoms such as depressed mood, psychomotor retardation, loss of interest, feelings of guilt, insomnia, anorexia and functional somatic complaints, when effective they benefited similar conditions. When an antidepressant is effective, it cannot be stopped until the depression has been resolved. Discontinuation of the medication before three months after maximum improvement, invites the risk of relapse. Ideally, dosage should be lowered gradually, and the drug not withdrawn until the patient has been well for four to six months. A resurgence of depressive symptoms may occur when the dosage is reduced, necessitating resumption of the previous therapeutic dose for several more months.

It is apparent that protracted antidepressant therapy is needed for many patients. This is especially true for those manic-depressives who have repeated melancholic episodes at close intervals. Clinical evidence to date strongly suggests that the judicious prescription of antidepressants may immeassurably benefit the victims of recurrent depression for, by maintenance therapy, they may at last be rid of protracted depressive suffering. There is little doubt that prolonged antidepressant therapy in such instances is preferable to repeated courses of ECT. The laboratory evidence implies that long-term antidepressant therapy is reasonably safe.[5] There is a clinical risk associated with the indefinite administration of the amine oxidase inhibitors because of the cumulative action of these pharmaceuticals. Although reversible, the effects of these enzyme inhibitors may last for several months.

The more common side effects of antidepressants are listed in Table II. Of the amine oxidase inhibitors isocarboxazid and phenelzine produce the most frequent and most serious side reactions. Nialamide causes the fewest side effects. Structurally, nialamide differs from the other inhibitors in that it contains a benzylcarboxamide group. It has been suggested that it is this part of the molecule and the manner in which nialamide is metabolized that accounts for its paucity of side reactions.[6] Amitriptyline and imipramine induce similar side effects but, generally speaking, those of amitriptyline cause less subjective discomfort in patients than those of imipramine. This was especially noted by individuals treated with both drugs.

TABLE II

Common Side Effects Due to Antidepressants

Side Effects	Amitriptyline %	Imipramine %	Isocarboxazid %	Phenelzine %	Nialamide %
Headaches	6	15	12	12	10
Dizziness	20	36	40	42	3
Blurred Vision	20	20	26	20	2
Dry Mouth	60	42	36	40	4
Postural Hypotension	0	2	8	6	2
Epigastric Distress	4	8	14	18	2
Constipation	60	40	10	30	3
Delayed Micturition	0	2	3	2	2
Altered Erotic Desires	0	7	9	6	1
Weakness and Fatigue	20	34	37	30	9
Sweating	16	33	9	12	4
Muscle Tremors	6	9	0	0	0
Number of Patients	130	100	100	100	100

The type and frequency of side effects are related partly to dosage, but mainly to individual susceptibility. Every patient had some somatic reaction to these drugs, but some had many on very low doses; others had a few minor ones on very high doses. Moreover, some individuals had side effects early; others only after they had taken the medicine at least two weeks. Age influenced the incidence of side reactions. The older the patient the more likely were they to occur, especially dizziness, postural hypotension, altered bowel function, delayed micturition, edema, and muscle tremors.

Most side effects of these drugs were not serious, seldom required counteracting measures, and subsided as the medication was continued. Some side reactions were potentially serious and warranted either remedial action or prompt discontinuation of the responsible agent.

Comment

Although each of these drugs is an antidepressant, there is considerable variation

in their therapeutic efficacy and safety. The results cited indicate that the non-amine oxidase inhibitors, amitriptyline and imipramine, are safer and more effective than the amine oxidase inhibitors, isocarboxazid, phenelzine and nialamide. Another major difference between these two groups of compounds, and one of utmost practical importance in this era of polypharmacy, is their dissimilar pharmacologic actions. The amine oxidase inhibitors potentiate opiates, atropine derivatives, barbiturates, ganglionic blocking agents corticosteroids, and antirheumatic compounds. They enhance the hypotensive effect of the oral diuretic compounds, chlorothiazide, and hydrochlorothiazide. They sensitize patients to the release of histamine, to novocaine and to anesthetic agents. They cause normocytic and normochromic types of anemia in some individuals. They are more apt than the non-amine oxidase inhibitors to unmask underlying psychopathology, especially schizophrenia, and to provoke a state of toxic psychokinetic stimulation or a toxic confusional state. These reactions may not appear until the patient has taken the drug for weeks or months. Admittedly, these toxic psychopathologic reactions to the amine oxidase inhibitors have been infrequent, but when they happen, they definitely cause the patient considerable ancillary difficulties and are a problem in subsequent psychotherapy.

These attributes of the amine oxidase inhibitors limit their usefulness and their range of therapeutic application. It is commonplace today for patients to be receiving several drugs simultaneously. Possible toxic somatic and psychopathologic reactions must be watched for when an amine oxidase inhibitor is added to a patient's medication schedule. Even when an enzyme inhibitor is the only drug an individual is receiving, it is mandatory for the physician to look for evidence of cumulative action and to give careful attention to dosage requirements. A therapist who uses an amine oxidase inhibitor cannot be casual about his ministrations to his depressed patient. He must insist on very close supervision of his office patients. He must limit the number of tablets his prescription calls for and not permit refills.

When a patient is a slow responder to an amine oxidase inhibitor, it is not uncommon for the practitioner to substitute another antidepressant or to combine it with another antidepressant with the hope of expediting recovery. This technique of therapy can be dangerous, especially when an enzyme inhibitor is replaced by a non-amine oxidase inhibitor such as amitriptyline or imipramine or a combination of either of these drugs and an amine oxidase inhibitor is prescribed. In some instances this has produced severe dizziness, tremulousness, restlessness, excitability, visual hallucinations, profuse sweating, collapse, hyperpyrexia, and death.[7] These reactions have been reported only when an amine oxidase inhibitor is replaced by amitriptyline or imipramine. They have been demonstrated repeatedly in various animal species.[8] Because the effects of an amine oxidase inhibitor persist for some time after the medicine is discontinued, it is necessary to wait at least a week before a patient can be treated safely with amitriptyline or imipramine. This can be most undesirable. It would seem preferable, therefore, to start depressives on a non-amine oxidase inhibitor to avoid this situation in the event the patient is unresponsive to the drug and another antidepressant is required.

Amitriptyline and imipramine are not innocuous compounds. However, in contrast to the enzyme inhibitors, they do not potentiate most of the commonly prescribed drugs, so they can be administered conjointly with whatever other medicines the depressed patient requires. They do not sensitize patients to the release of histamine, to novocaine, or to anesthetic agents. These non-amine oxidase inhibitors are not cumulative and are not particularly prone to precipitate toxic psychokinetic stimulation even in schizophrenics, unless the patient is overdosed or these drugs are given inadvertently to patients totally unsuited for them. The effects of these compounds disappear promptly when the medicine is stopped. Clinical experience with amitriptyline and imipramine has revealed them to be especially safe for protracted administration with little physical or psychic hazard to the patient. The over-all management of individuals on amitriptyline or imipramine is much easier than it is when the amine oxidase inhibitors are employed.

It has taken several years to elucidate

the exact place of these antidepressants in the treatment of depression and their usefulness and safety for the practicing physician. There is little doubt that these compounds, especially amitriptyline and imipramine, represent true advances in the treatment of melancholia. They are effective and are particularly suited for the treatment of pure endogenous depression. Fewer mistakes will be made and more favorable results will be achieved if they are not prescribed for every type of depression, but reserved for those patients for whom they are indicated. The proper prescription of these drugs produces progressive disappearance of the signs and symptoms of depression. Many of the factors that favor a satisfactory response to these drugs are also those clinically associated with the expectation of a good reaction to ECT. The danger lies in their general slowness in taking effect which makes their use hazardous for severely depressed suicidal patients who, preferably, should be treated with electroshock therapy. Otherwise, these compounds can be a satisfactory substitute for shock therapy for most depressed patients. Thus, these drugs have lessened the need for ECT. On those occasions when ECT is necessary, if the shock therapy is combined with an antidepressant, ECT can be dispensed with after a few treatments.

Although it is not possible in this brief allocation to state all the reasons for this observation, it is my considered judgment that the future of hydrazine amine oxidase inhibitors is dim indeed. Unless there is an improvement in this type of medicine, they will become obsolete because of their limited usefulness and the hazards of their prolonged administration. Thus, they will be driven from the market and join iproniazid and pheniprazine on the shelf of discarded pharmaceuticals. At the moment and for the immediate future, it appears to be more advantageous and safer to treat melancholic individuals with amitriptyline or imipramine. This is not a detraction from the amine oxdase inhibitors, for, although of restricted therapeutic usefulness, they have contributed much to our knowledge and understanding of the physiologic and neurologic foundations of human behavior.

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Isocarboxazid is available under the trademark Marplan®, phenelzine under the trademark Nardil, nialamide under the trademark Niamid, imipramine under the trademark Tofranil®, amitriptyline under the trademark Elavil®.

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Antidepressives: The Pith of Affective Therapy

JOHN C. SAUNDERS, M.D.*

Early in the 16th century, after 2000 years of relative stagnation of European technology, a scientific and industrial revolution occurred which began the transformation of the mental outlook of mankind and its material way of life. This transformation is being effected only now in many parts of the world as we are becoming aware through the radio and television reports on United Nations sessions dealing with problems of developing countries.

In the mid-twentieth century, another revolution began with the advent of the tranquilizers into psychiatric therapy in 1952 and psychic energizers in 1957.[1] The organic concept of psychiatry, however, has received only tacit recognition as yet. The history of American psychiatry shows that 100 years were needed for the Freudian philosophy to become the dominant force; today we must ask how long it will be before psychiatry experiences the effect of the pharmacological revolution. I raise this question on the basis of observations and operations in the field of psychiatry since 1952. Today, after nine years, the great majority of psychiatrists fail to understand the known pharmacology, neurophysiology, biochemistry and psychological phenomena of commercially available phrenotropic drugs.

Unfortunately, there are no hospitals or medical centers where adequate drug evaluation including both clinical and laboratory studies can be carried out. Since this meeting is sponsored by a research association, I feel it my responsibility to bring this problem to your attention. Only a few examples will be given: administrative inefficiency and interference unduly delay construction and research programs; jaundice and liver failure may be observed with both the tranquilizers and energizers, yet inadequate laboratory studies have been made; there are frequently neurological signs and symptoms, yet spinal fluids are almost impossible to obtain; in treatment, obviously severely depressed patients are given a highly sedative tranquilizer instead of an energizer; the post-mortem follow-ups of treated patients is completely inadequate both in number and in procedure. We have therefore failed to obtain this and other needed data. The physicians in residency for specialized training are not being taught neuropsychopharmacology, probably because the staff does not know how and positively because of indifference. The remark I hear frequently when the question of indifference to drug therapy is raised goes something like this, "The probability that the drugs are doing anything other than covering up the symptoms is remote."

This type of criticism indicates failure to understand the usefulness of the drugs or the correctness of the theory that the phrenotropic drugs demonstrate antipsychotic effect; its proof rests on their being tested by experiments designed to challenge the theory as in all scientific investigations. It is important that we be cognizant of the fact that every important scientific theory must have a low probability; in other words, a high probability theory will be of little scientific value, since it states too little. Yet vast sums of money and time are expended on these insignificant investigations of high probability values. The drugs provide for new techniques and new theories that are testable, and psychiatry needs such theories.[2]

We cannot make the progress necessary and possible if the hospital setting maintains a dichotomy of scientific research and the usual clinical program. These are not compatible and hoping that they will soon become compatible has not made them so. The failure is not that we have too many drugs to evaluate, but that our approach to the problem remains both inadequate and largely non-scientific because of what I would diplomatically call *scientific inertia*.

Discussions beginning in 1952 with psychiatrists in private practice, made me aware of the large number of treatable cases of depression being seen by all physicians. Many admitted overlooking the diagnosis of depression for long periods of time. These

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cases were not the obvious severe depressions that received early psychiatric treatments; they were the cases where depression was only a symptom and was masked by other signs and symptoms. The diagnosis was nosological rather than phenomenological; therefore, that of depression was not properly considered and the patients were improperly treated. Why do I say this? Because today the problem is the same. We are continuing to receive in our state hospitals the failures of the present, resulting from errors both in diagnosis and therapy and both are continuing to be made in the hospitals.

Pharmacology offers the psychiatrist both new theories and new methods. Frequently, however, he continues to rely on myths rather than learning the contributions to psychiatry made by the basic medical sciences. Many are aware that the practical benefits of the tranquilizers are not complete and leave the patient on a plateau.[3] It is also known that the antidepressive drugs have an even narrower spectrum of clinical activity and may bring about exacerbations of aberrant psychic processes in man frequently resembling acute schizophrenia.[3,4,5]

A look backward is essential to obtain a historical perspective for our comprehension of depression since too many myths exist in the understanding of the condition today. Guislain[6] assumed that every mental disorder was preceded by a more or less pronounced stage of depression. Zeller[7] and Griesinger[8] agreed with Guislain that most mental diseases commence with depression and Griesinger had no hesitation in speaking of the *stadium melancholicum* as the initiating period of mental disease. Magnan[9] states that "one finds the most unexpected combinations of mania and melancholia in the same patient." Not only are the signs and symptoms mixed, but many of the early psychiatrists, including Kraepelin, declared that for practical and didactic purposes labeling with names of disease is unnecessary.[10] Burrows[11] stated: "The best rule, however, for everybody to observe when attempting a judgement on any particular case of insanity is to take care and preserve his own faculties clear, and as free from mysticism of speculative philosophy as from the trammels of nosology." The problem is to improve our ability to diagnose, treat and discover more effective drugs for neuropsychiatric diseases. Since the etiology remains unknown, we cannot continue to use nosology but must apply phenomenological criteria if our acumen is to improve to the level of defining homogenous categories for the comprehensive biological approach required to understand depressive states.

We have proposed that we return to the essential factors of a disease—signs and symptoms: the symptoms of depression can be classified as primary and secondary, the signs as visceral, autonomic, endocrine and metabolic.[12] The primary symptoms include melancholia, sadness, despair, dejection, a dearth of psychic energy and mental productivity as indicated by fear of initiating new activities and psychomotor retardation or agitation. The secondary symptoms are characterized by delusions of persecution, feelings of depersonalization, hypochondriacal complaints, obsessive-compulsive behavior, hallucinations and suicidal tendencies. The signs are anorexia, constipation, dryness of mouth, insomnia, impotence and a reduction in menstruation.

Many who still use the older methods, such as electric shock, modified insulin treatments, psychosurgery and sleep, fail to learn the proper use and value of the new antidepressive drugs. If these older methods were so effective, why is the suicide rate growing higher; our present rate is over 18,,500 per year in this country and 5,000 in England. The tragedy of this situation is that depressive states are now the most easily treatable and they have the greatest probability for recovery of all neuropsychiatric disease. In order for the patient to obtain freedom from depression two criteria must be met: correct diagnosis and intelligent treatment. If a proper understanding of the antidepressive drugs existed among psychiatrists and other physicians, it would make possible an easy and effective means of treating most depressive states by all physicians. Many clinical studies have been published during this century, but they are largely occupied with statistics and semantics that resulted in bickering about minutiae. I appeal for a return to the primary factors, because all medicine rests on signs and symptoms. To administer the currently

available antidepressive agents properly may free the patient of his disease.

In addition to the older forms of therapy previously listed for depression, we believe there are several other and better choices: the monoamine oxidase inhibitors (hydrazines and nonhydrazines) and preparations such as imipramine and amitriptyline, that may act by sensitization and activation of central adrenergic mechanisms chemically at the submolecular level. These drugs may be used alone or in combination with the tranquilizers. This combination is frequently essential for maximum therapeutic efficacy in schizophrenics with depression or with the presence of the primary symptoms of affect described by Bleuler: disturbances of affectivity, autism with a detachment from reality, associational deprivation and ambivalence of affect and will.[3,12-14] These antidepressive agents also alleviate anhedonia following the prolonged use of reserpine and the phenothiazines.[4,15] The use of presently available monoamine oxidase inhibitors and imipramine may exacerbate the signs and symptoms of a psychosis in a limited number of cases. They also are associated with untoward effects that prevent many physicians from administering them in a non-hospital setting for lack of adequate control. Previously, we have reported on the clinical efficacy of amitriptyline alone and in combination in the control of depression as a symptom or as a disease entity.[12,14]

Amitriptyline is an effective antidepressive agent in depressive states including schizophrenia with depression. It can ameliorate both primary and secondary signs of depression and schizophrenia with varying degrees of effectiveness. Its primary action in hospitalized psychotics is antidepressive; this along with its very low rate of side actions make it a drug of potentially frequent application in a broad spectrum of neuropsychiatric diseases. We believe you will find it advantageous to read our publications on its use alone[12] and in combination[14] in long-term hospitalized schizophrenic patients with depression. Since a large part of any hospital population will reach a plateau if given only a tranquilizer or an energizer, we suggest that amitriptyline alone be given prior to combination therapy, as this drug is easier and safer to administer and produces a significant improvement in a high percentage of cases (60-75).

Conclusions

1. It appears necessary to classify psychoses into two classes, affective and ideational, if the proper phrenotropic drug is to be given. The tranquilizers are most effective in ideational psychoses and the antidepressive agents for the affective disorders. General as it may appear and provisional as it should be, this tentative classification is better than implying a finiteness of knowledge we do not have which can in itself prevent an advance in knowledge.

2. It is possible now to select drugs for the alleviation of either Bleuler's primary or secondary symptoms of schizophrenia. The antidepressive agents alleviate the primary and the tranquilizers control the secondary symptoms. The preparation amitriptyline is most effective in controlling the primary symptoms and, since it is relatively free of untoward reactions, it provides us with an important treatment for the disease of depression and aberrant affect in all nosological classifications.

Imipramine is available under the trademark Tofranil®, amitriptyline under the trademark Elavil®.

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Masked Depression

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The recent impact of the newer psychopharmaceutical agents has not only brought psychiatry closer to medicine, but has also brought medicine back to the psychiatrist. These two distinct and apparently divergent disciplines have too long been separated because of language differences and difficulties in communication. Psychopharmacology, because of its neurophysiological, biochemical, metabolic and psychodynamic roots, will eventually narrow this once wide divide. Perhaps the physician, no matter how he is labeled because of the ever increasing needs for specialization, will once again understand, even if he cannot always cope with the "total" treatment of the "total" patient. Body and mind, fortunately, are usually fairly well attached[1] and often so intricately intertwined and interwoven that the combination can at times defy the best intentions of some specialists, not only to separate them, but to subdivide them into smaller and smaller compartments.

In considering the problem of emotional depression, it is apparent that many patients require specialized psychiatric opinion and treatment. Their management will depend upon various factors: the depth, length and nature of the depression; the accessibility of the patient; the evaluation of potential suicidal intent; the orientation, philosophy, experience, training and convictions of the individual psychiatrist. A patient with depression may appear to be relatively accessible to one psychiatrist and seem to be less accessible to another. Although this fact is natural and human, it creates agitation at psychiatric meetings. It also produces considerable confusion in the psychiatric literature since it plays havoc with the percentages labeled as "cured," "effectively reached," "less effectively reached," "fair" and "no effect."

Because of these difficulties, many psychiatric investigations are often labeled as "unscientific and suffering from a lack of objectivity." Its severest critics are completely oblivious to the fact that the same situation may occur in other areas of supposedly more objective clinical investigation.

For instance, if patients with peptic ulcers were to be investigated, it would be discovered that some ulcers are small, while others are large. Some can be demonstrated radiographically, while others defy the best diagnostic techniques. Some fail to be visualized, yet perforate, showing a complete disrespect for erudite opinions based on scientific facts. Small ulcers of recent origin may penetrate, yet large ones may clear completely within six weeks. Some ulcers become chronic and intractable, eventually necessitating gastric resection, irrespective of their depth, dimensions and length of treatment, despite the experience and specialized training of the physician and the apparent cooperation and accessibility of the patient. Cures can often be obtained by many diverse medications, modalities and techniques, especially if patients are treated promptly.

As for depressions, some are minor, others more severe. Some can be demonstrated easily, while others are "masked" and hidden because of the patients' need to deny this affective state. Some patients fail to be properly evaluated, and become successful suicides. Here, too, there may be a lack of respect for those opinions which failed to indicate such danger. Depressions may be of recent origin, appear to be minor, yet become quite severe. Severe depressions may clear in less than six weeks—but here our analogy with ulcers may fall short because this is often predictable in the treatment of endogenous depression with ECT. Some become chronic and intractable despite the experience and specialized training of the physician and the apparent cooperation and accessibility of the patient. Cures, too, can be produced by many diverse medications, modalities and techniques, especially if reported promptly.

In the management of depression, the major current approaches include psychoanalysis, psychotherapy, electroshock treatment (ECT) and pharmacotherapy.[2] Each

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has its exponents, and opponents—yet strangely enough, many patients do recover irrespective of the modality used. Perhaps, in some, it is not the modality, the pill or the technique, but the personal attributes of the physician that produce the results. The greatest variable of all is the patient, since no two are alike, and often the same one is different on successive occasions.

In reporting on patients with "masked" or hidden depression, an additional variable is added, since this entity is not readily apparent. Medical help is usually sought at the hands of the non-psychiatrist. It is often only because of the pressure of the referring physician, or frantic relatives, that the psychiatrist is eventually consulted. A characteristic and pathognomonic sign is the patient's vehement insistence that the somatic complaints represent a definitive, though still undetected medical illness. In some, definitive organic illness is eventually discovered. Whether this is major or minor, possibly related or completely irrelevant, both the patient and the doctor feel relieved, since there is something "tangible" to treat. Unfortunately, specific as well as nonspecific remedies, sometimes inclusive of surgical intervention and extirpation of diseased organs, are to no avail. The patient's failure to recover becomes understandable only when both patient and doctor realize that the somatic illness has not been the cause of the complaints and disability. The emotional depression must be treated, but this is difficult to accomplish if it is not recognized. Too frequently it is completely submerged by the somatic symptoms or illness, roentgenographic and electrocardiographic investigations, and multiple laboratory reports.

This report will be limited for the most part to an analysis of patients treated with amitriptyline, an imipramine-like antidepressant, as part of their "total" management. Time does not permit an adequate evaluation of all the other antidepressants utilized in this over-all study. Subsequent reports will consider their effects and will attempt to point out that different antidepressants seem to have different spectra of action. For example, imipramine derivatives, such as amitriptyline and imipramine, seem to be more efficacious in agitated depressions, while the amine oxidase inhibitors, iproniazid, isocarboxazid, phenelzine and ethyltryptamine, seem to be better in pure retarded states.[3] The patients in this study were all ambulatory, treated either in private practice or in a psychosomatic clinic.

In the 25 patients treated up to the time of this report, the most frequently observed symptoms were generalized vague somatic complaints, tiredness, insomnia, abdominal pain or spasms, headache, palpitations, and cardiac awareness. Somewhat less frequent symtoms included nausea, vomiting, diarrhea, pains in the legs, neck pain, dizziness, cancerophobia, difficulties with dentures, bitterness in the mouth, and heartburn.

As for the findings of coincidental definitive medical illness, no single disease entity was outstanding. In this series, the illnesses included peptic ulcer, hypertension, spastic colon, coronary disease, diabetes, arthritis, obesity, alcoholism, cataract, glaucoma, Hodgkin's disease, colloid goitre, radiculitis, prolapsed uterus, hyperthyroidism, and hypogonadism.

In some patients, symptoms were present with or without concomitant proven illness; in others, multiple illnesses were found.

As for auxiliary treatment, in addition to amitriptyline, some received electroshock therapy, others only minimal supportive therapy and still others received more formal psychotherapy. Some received one form of treatment (electroshock), which was subsequently followed by another (psychotherapy). In evaluating the effectiveness of amitriptyline in all these different settings, it was considered to be effective in 17 of the 25 patients (68%).

Eight of the 17 patients did well with the drug alone, with only the barest and most minimal psychotherapy. This technique was utilized in these patients because it fit the patient or the setting of the treatment. The dose varied from 100 to 150 mg. a day, and the length of time required varied from two to six weeks. One of them was sick enough to warrant electroshock therapy, but after a single treatment she became cyanotic. She subsequently responded to amitriptyline alone. One had recently recovered from severe hepatitis while receiving iproniazid. She responded to amitriptyline within two weeks. She has been taking the drug since August 1959; although she feels well and looks well,

she refuses to discontinue the medication. Many times one feels the temptation to switch to the placebo to prove whether she really needs the drug or not, but as yet this temptation has been suppressed. In another, electroshock was considered, but held in abeyance because of severe glaucoma. She promptly recovered within six weeks on amitriptyline and subsequently maintained her improvement during the trauma and stress of eye surgery. Three in this group who were treated with the drug alone did well, only to relapse. One was a 65-year-old spinster with a multitude of complaints which defy description, who also had a few proven definitive medical illnesses (arthritis, peptic ulcer, hypertension). She had been attending the OPD at Maimonides Hospital regularly for at least twenty years. There were two periods of hospitalization elsewhere for electroshock therapy. Her thick chart indicated that she had been exposed to various clinics: medicine, arthritis, gastrointestinal, hypertension, cardiac, orthopedic, physical medicine, rehabilitation, etc. It was not too difficult to arrange for her referral and transfer to the new Psychosomatic Clinic. At the first interview, when queried, she stated she was not depressed, but cried only because her "feet were painful." She was treated with amitriptyline and promptly responded within two weeks. The crying ceased; her feet "still hurt but they didn't bother her." However, within six weeks she relapsed. She has since been shifted to various other antidepressants and has shown a similar pattern of response. She now states (after 10 months) that she feels there may be some hope. Another was advised that electroshock therapy was definitely indicated; she refused and promptly responded to amitriptyline. She did well for about eight weeks and stated she felt "fine"; however, her husband said she was once again "absolutely impossible," that she didn't sleep, cried constantly, and did not attend to her responsibilities. When the possibility of electroshock was again suggested, she failed to keep her next appointment. The third and last in this category had suffered with persistent root pain following a lipiodol injection into the spine twenty-five years before, and had roentgenographic evidence of nerve root infiltration. A neurosurgeon advised lobotomy because of persistent pains which had resisted all previous therapy. She was then referred for psychiatric treatment because this seemed to be the lesser evil. She was treated with amitriptyline and responded within two weeks, to everyone's amazement, but within six weeks, unfortunately, she relapsed.

Five of the 17 in whom the drug was effective, were also given electroshock concomitantly (6-8 treatments). All did well; three have been followed for at least six months with minimal psychotherapy.

Four of the group received amitriptyline plus more formal psychotherapy with excellent results and no relapses. In two, a short-term period of therapy (4-6 weeks) sufficed to produce dramatic changes. The two others remained in psychotherapy for 3-6 months (once weekly) and made substantial gains. In each of these instances, it was clear that the drug was synergistic with psychotherapy and enabled the therapist to tackle the deeper personality problems.[5]

In considering the eight failures, two remained on the drug for only a few days. One stated she developed a "nervous" tremor which, incidentally, had been observed on numerous occasions over the past two years. It was not Parkinson-like and was not relieved by anti-Parkinson drugs. A second patient developed a pruritic rash within two days. Two additional patients were treated from 7-10 days and decided to stop the medication. In one, the complaint was of "too much relaxation," which can indeed be disconcerting to a confirmed hypochondriac.

Two patients showed no response within two weeks and failed to return. Only two of the eight failures remained on the drug for at least four weeks. These two had showed no agitation. They were shifted to phenelzine and responded within a few weeks.

Discussion

Masked or hidden depression is characterized by the presence of varied somatic symptoms, and is often accompanied by concomitant somatic symptoms and/or proven medical illness. Most of these patients deny their subjective feelings and prefer to continue their search for an organic diagnosis. When organic illness is found, both the doctor and the patient usually feel better; yet specific

as well as nonspecific measures directed towards alleviation of the medical illness, unfortunately, do not result in an amelioration of complaints. Too frequently, this lack of recovery is related to an underlying undiagnosed depression. Both the patient and the doctor become unilaterally preoccupied with the search for organic illness, its evaluation and re-evaluation, and its treatment, without a concomitant evaluation of the patient's emotional status. Yet, failure to diagnose a severe depression may be as disastrous as failure to diagnose an acute coronary occlusion.

Some of the clues to the presence of a hidden depression can emerge from the history, which should always include an interview with at least one in the family besides the patient. A history of cyclothymic mood swings either in the individual or in the family history, previous episodes of depression, or previous treatment with electroshock, are all pertinent. A history of previous flare-ups of somatic illness during periods of stress is most significant. Recent death or illness of a relative, or close friend, or employer or employee, may precipitate a depression through its release of ambivalent feelings.[6] Financial difficulties, the failure to live up to one's ideals and expectations, a loss of prestige, or even a sudden success may set the stage for the need for self-punishment and expiation, as pointed out by Rado.[7] Birthdays, holidays, anniversary reactions to parent's death[8] are possible provocative factors.

Sadness may be evident but is often covered by a disarmingly inappropriate smile. Attempts to engage the patient in conversation in order to evaluate emotional trends, are frequently blocked and countered by constant and repetitive organ symptom recital. These symptoms are characteristically vague and generalized, and rarely follow known disease patterns. Sleep disturbances and changes in appetite and weight can often be elicited without too much difficulty. Their presence, although meaningful for the alert physician, may not spell out depression for the patient. These clues are easily elicited while the basic depression is denied.

In the management of hidden depression, an evaluation or re-evaluation for possible organic illness may be indicated. The possibility of an occult malignancy (especially in the lung, pancreas, or brain), or lupus erythematosus must be kept in mind. Patients with recently discovered diabetes, coronary disease, peptic ulcer, hypertension, etc. may suffer depression because of somatopsychic reactions. Here the discovery of the medical disease often produces an understandable emotional reaction even in relatively stable persons, but does not negate the need for primary treatment of the depression if this reaction is persistent and severe.

Conclusions

1) The impact of the era of psychopharmacology on the integration of medicine and psychiatry has been considered.

2) Some of the pitfalls in the investigation of these newer drugs are evaluated.

3) The current treatment and approach to the management of depression have been considered, with special emphasis on the problem of "masked" or hidden depression, where somatic symptoms and/or disease mask the emotional overlay.

4) Results with amitriptyline, a new antidepressant, with or without other concomitant modalities of treatment in the total management of depression, are considered. A full consideration of the effects of various other antidepressants may eventually delineate their respective areas of usefulness.

5) Some of the difficulties encountered in the evaluation of pure statistical reports are illustrated by representative case studies.

6) The need for investigation for possible concomitant medical illness is not negated; but the need to discover and treat underlying depressive illness is emphasized.

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DISCUSSION OF DR. DORFMAN'S PAPER

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There can be no disagreement about the ubiquitousness of depression. Every clinician has seen cases which can be subsumed under the name of masked depression when he is pressed to consider the indications for the various drugs which have been suggested as useful in different types of depression. As Lehmann put it, "The introduction of some of the new psychoactive drugs has caused a certain confusion among psychiatrists in regard to the term depression." He has proposed a differentiation of depressed states on the behavioral level when only a reduction of spontaneity is the criterion. Again, the need for a frame of reference has led Alexander to classify the "four main subtypes of depression with a differential response to drug therapy." These formulations are certainly thought provoking. Their verification and widespread acceptance awaits further observation.

Alexander's classification appeals to me because it is the kind of approach which must come—the marriage of psychodynamics and psychopharmacology. However, since I have not yet confirmed Alexander's formulations to my satisfaction I have used another frame of reference to evaluate my observations on a specialized use of amitriptyline (namely, parenteral and particularly intravenous) in various types of depression with the reduction of spontaneity being the common denominator.

The rationale for parenteral use derives from the universal objectives which I feel hold for all psychotherapy: (1) to establish emotional contact with the patient; (2) to modulate the patient's affects because words are used essentially as carriers for affects in therapy, and affects are the "prime movers" in treatment.

Of 40 patients, ranging in age from 18 to 70, 33 were given one or more intravenous injections of amitriptyline. The usual dose was 15 mg. and the maximum dose was 30 mg. The side effect of drowsiness determined the desirable dose. Undesirable effects on pulse and blood pressure were not noted. The descriptive term "relaxed" was usually applied by the patient to his subjective state within 15 minutes after the injection. It was noted that the same feeling was reported in three patients with tremors of the senile type although the tremors did not cease. In a small number, daily intravenous injections were given for a week or more. In 90% of these cases, the oral preparation in doses of 75 to 100 mg. for 24 hours was also administered.

Even the purely somatic ECT serves the purpose of facilitation of emotional contact. However, ECT may be threatening enough to the patient to impair its value in paving the way for a more relaxed doctor-patient relationship. This drug response of "the relaxed feeling" noted after parenteral amitriptyline was used to abet therapeutic rapport in addition to its specific antidepressant effect. Significantly, the modulation of affect thus seen did not achieve that affective quality which would suggest that amitriptyline was a euphoriant. This struck me as being significant in that Dr. Dorfman notes the difference in effect between amitriptyline and the MAO inhibitors while Dr. Hoff previously made an analogous observation on the effect of imipramine therapy compared with that of the euphoriant effect of iproniazid.

In the above patients as in Dr. Dorfman's series, other procedures, including ECT or other psychopharmacologic agents, were used. Having seen the positive response to amitriptyline alone in some patients, I was interested in the possibility of the combined approach of amitriptyline with other agents. No contraindications were noted.

My observations on amitriptyline suggest that the modulation of affect possibly encompasses a change in the level of tension and thus may be particularly related to an antianxiety factor. It would seem that this drug is singularly safe for use in the aged or in chronic brain syndromes in the doses mentioned for parenteral usage.

I am in full agreement with Dr. Dorfman as to the use of amitriptyline in the total treatment of the depressed patient (of the masked variety and other types). Furthermore, the evolving categories of depression and the unsettled status of specific drugs for a specific type of depression has led me to try amitriptyline parenterally to facilitate emotional contact in all varieties of depressed patients. It was noted that the lack of side effects has made available a safe and useful drug without regard to the type of depression treated.

The Treatment of Depression in Private Practice

EDWIN DUNLOP, M.D.*

The central theme of "anxiety" has characterized so much of our living as well as the literature, drama and music of recent years, that the era was well dubbed the "age of anxiety." Today, however, evidence which includes an increasing number of reported suicides, seems to indicate that the age of anxiety has passed and is being replaced by a "decade of depression."

We are given to understand that 25,000 successful suicides are reported annually. One might presume that an equal number of suicides are dismissed or passed off or hushed up under another guise by those who desire to remove the social stigma associated with their demise. Karl Menninger has estimated, that for every successful suicide in the United States, there may be 60 unsuccessful attempts. Many of us have treated patients who have made multiple but ineffective suicidal attempts during their psychiatric careers. If the assumption on Menninger's part is correct, we can deduce that three million Americans each year make some attempt at felo-de-se. Even lowering this rate to one-half of the estimate, suggests a figure of over one million and is numerically significant. It is the fifth most frequent cause of death in youngsters age 15 to 19 and is the third largest cause of death among the college population.

Bennett, in a recent article in the Journal of the American Medical Association, reported on 150 patients who had been exposed to medical or surgical procedures and were eventually recognized to have various psychiatric disorders. More than 50% of these, 85 in all, had depressive illnesses. The word depression is loosely used both in diagnostic and descriptive terms and it is evident that it is not a descriptive entity but a multiheaded monster with vulnerability to specific and select treatment. Depressive illness in its multiple manifestations is the most common and the most challenging problem that confronts the psychiatrist in private practice today. If it is such a problem to the psychiatrist, how much more difficult and how frequently unrecognized is this condition in the general medical population?

Our topic today is indeed indicative of the need that must be met. All of us, I am convinced, are aware that more and more of our patients are showing depressive elements to their illnesses and it has often been remarked recently that reactive depressions are on the increase, while there seems to be a definite diminution in the percentage of the classical manic-depressive and involutional type depressions.

In spite of the apparent decline of manic-depressive psychosis, which carries a percentage risk of 1% of the male population, it may be presumed that from 5 to 10% of the male population at one time or another and possibly much more of the female population, show varying manifestations of depression. This would indicate a population of between eight and ten million people depressed at this moment. Although many of these are mild depressions and we recognize they have the virtue of spontaneous remission, in due course of time the depressed patient nevertheless becomes a problem to his family, a burden to his physician and a danger to himself.

Treatment: The treatment of depression has been alluded to by other prominent authorities and a great deal of repetition will be avoided if one leaves out the classical descriptive signs, symptoms and behavior of depression and pass on to therapy.

By the time the average patient seeks psychiatric help, he has been exposed to a blitz or a barrage of platitudes by well meaning and well intentioned friends who unanimously agree that the patient "must help himself," "snap out of it," "has to forget himself," "stop worrying," "go out more," etc. This of course is gross medical and psychiatric ignorance at its best, and succeeds only in plunging the patient into more detachment and despair.

At the earliest possible time, the patient must be assured that self help is of little value, that the problem is one of cooperative management and that a successful outcome can be anticipated in the light of pre-

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vious experience. At this point, stress should be removed from the patient by those who persist in such platitudes and the patient should not be exposed to further insults by any attempt at systematic psychotherapy. This would serve only to deepen the patient's sense of futility and despair.

It is important, however, that the therapist should establish a warm rapport with the patient at the earliest moment. This is not an easy art and requires much patience and skill. The approach must be optimistic and positive with constant reassurance about ultimate recovery. The patient often responds to this and constant repetition of the theme gradually bears fruit.

It is somewhat dangerous to set time limits on a patient's recovery, as failure to achieve improvement by a designated date may plunge the patient into further despair. The approach must be warm, personal and sincere. No better description of the care of the depressed patient can be given than the words of the late John Donnelly, "To care for a patient, you must *care* for him." This can only be accomplished if adequate time is spent in making contact with the patient and gaining his confidence. Constant reassurance about the recoverability of the illness and the explanation that most of the self-accusatory, malignant and morbid ideas are generated by the illness itself may appear to make little impression on the patient, but these are often recalled gratefully by the patient after his recovery. To remain cool, aloof and objective or, as Jack Ewalt says, "To make like an analyst," is only to be deplored and has no place in the treatment of depression.

The current era is replete with an array of antidepressant therapies the number of which has never been available before. To the amine oxidase inhibitors as a group must go the credit of producing a multitude of satisfactory recoveries. This group, however, is but the entering wedge. Modifications and variations are constantly being produced which successfully increase the effectiveness of the antidepressant drug and at the same time decrease the untoward or undesirable reactions. It must not be forgotten that different drugs are effective in different types of depressions. This indicates that we are dealing with symptoms rather than separate disease entities.

Severe depressions are best handled under hospital conditions and should therefore be admitted to a psychiatric facility. This has the additional benefit of removing the patient from an environment which sometimes can be brittle with hostility. Not uncommonly, deep resentments and animosity toward close relatives appear during a depression, and a change of environment is generally beneficial for both sides. Hospitalization also provides the patient with a feeling of security. By submitting to hospital treatment, the patient is making a cooperative gesture. Adequate sleep must be encouraged, especially when early morning awakening is experienced. Most depressed patients will require two or three times the recommended dosage of barbiturates or hypnotics and should be given maximal dosage while under hospital protection to promote better sleep habits. Some of the milder nonbarbiturates such as glutethimide, 1 gm., and methyprylon, 600 mgm., can produce effective sedation.

Most patients complain about loss of appetite and frequently demand something to stimulate this, which is virtually impossible. Supplementary high potency vitamin therapy should be given and, as we are frequently utilizing amine oxidase inhibitors and other antidepressant chemicals which require adequate cerebral metabolism, special emphasis on adequate supplements of essential vitamins and amino acids have prompted me to provide all patients who are on antidepressants with a formula comprising the following: glutamine 300 mg., GABA 60 mg., niacin 10 mg., thiamine 10 mg., ascorbic acid 10 mg., pyridoxine 5 mg., acetylcholine 5 mg.

As far as specific therapy is concerned, where the depression is severe and suicidal risk is great, there is no better treatment than electroshock. It can be given with the concurrent administration of antidepressant agents. Our experience has been confirmed by others that the utilization of these chemicals affords an economy of ECT as the maximal therapeutic effect of the medicine and the treatment seems to peak at about the same time—toward the end of the second week. Once the initial course of electroshock therapy has proven successful, the pa-

tient can be released from the hospital and followed up either in the Out-patient Department or in the office. This, however, is a dangerously critical transition. The patient should be closely watched during the first week or ten days. Many of us have had the experience of an apparent recovered or improved patient who has sought permission to go home and has convinced his physician that he is now well and has promptly committed suicide at the first opportunity. Maintenance with an antidepressant drug is continued long after the patient has recovered. As a rule, maintenance therapy should be continued for a period of four to six months, during which time a patient should be seen regularly. At this stage, psychotherapy can be of immense value in preventing recurrence of the depression and in dealing with the patient who until this time was inaccessible for psychotherapy.

In treating the office patient who does not require hospitalization, the initial visit should provide the time for a fairly long interview. I use this opportunity to provide the patient some immediate symptomatic relief.

Intravenous amobarbital and, more recently, amytriptyline have very often produced a gratifying response which the patient experiences immediately. They also enable one to impress upon the patient the successful anticipated outcome.

Amitriytpline has become increasingly useful to me in the treatment of the depressed patient, especially the one who shows the secondary type of depression called the "smiling depression" by Roth and Sargant. These patients very often do poorly when given electroshock but are effectively treated when given antidepressant chemicals. Amitriptyline has a specific advantage over any antidepressant currently available and I see increasing evidence of its usefulness in reducing tension, agitation and anxiety, as well as in relieving the depressive quality of the illness. Amitriptyline appears, more by accident than design, to combine better than any other antidepressant drug the successful treatment of anxiety at one end of the scale and depression at the other. Experience in the past has shown us that, when using electroshock or analeptics, although depression can be relieved, the accompanying anxiety eventually proves more troublesome than the depressive phase of the illness. Amitriptyline successfully bridges these divergent symptoms which are displayed in varying proportions in all depressive syndromes.

Although closely related to imipramine, amitriptyline has shown none of the problematic side effects such as vasomotor flushing, sweating, palpitation and hypotension. In my experience, it has thus far not caused any excitation or agitation. Amitriptyline has been given to more than 20 patients by the parenteral route, generally in a dosage of 30 mg. intravenously at the onset of treatment. The same dose is repeated two to three times daily in the hospitalized patient until clinical improvement is obtained. This is not an attempt to establish a loading dose, but it has, to my satisfaction, initiated clinical recovery, and appreciable improvement is sometimes experienced by the patient in a matter of minutes. It is extremely well tolerated. The patients are able to leave the office or their rooms a short time after the intravenous injection and there has been no reported hypotensive complication.

Intravenous amitriptyline has been plotted on the Winston Blood Pressure Follower in the lying, sitting, and standing positions at three minute intervals without a variation of more than 10 points systolic pressure. It is gratifying to have patients show recovery and improvement with amitriptyline from other than depressive symptoms for which the drug was not primarily intended. Noticeably, there is a reduction in gastrointestinal distress, hyperventilation, dizziness, tension, and vasomotor dysfunction. This reveals a component of central nervous system anticholinergic effect which is operating with this compound. Relief of these symptoms is often noticed before the depressive element of the patient's illness has been affected.

Hospitalized patients tolerate 25 mg. p.o. q.i.d., and some have been given up to 200 mg. daily without adverse effect. There is commonly, however, a complaint of drowsiness when 100 mg. daily is administered. For office patients, it is surprising how many excellent results can be produced with a dose as low as 10 mg. t.i.d. This is most effective

in the neurotic type of depressed patient who generally overacts to phenothiazine tranquilizers and barbiturates and tends grossly to exaggerate the sedative effect of these compounds. Amitriptyline has not produced this to any degree in such patients. Other than the complaint of dry mouth and some constipation, very little in the way of side effects can be attributed to the medication at this low dosage.

Amitriptyline offers as much usefulness in nondepressive behavior as it does in a depressive reaction and it is intriguing to explore the broad spectrum of this interesting chemical compound.

Approximately one hundred and twenty patients have been studied with amitriptyline during the last fifteen months. It is an effective antidepressant when employed in both hospital and ambulatory patients. Its dependability and freedom from toxicity and severe side effects merit further evaluation on a broader spectrum of depressive disorders.

Glutethimide is available under the trademark Doriden®, methyprylon under the trademark Noludar®, amitriptyline under the trademark Elavil®, imipramine under the trademark Tofranil.

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Electrostimulation Therapy and Drugs

(A Future for Computers)

PAUL H. WILCOX, M.D.

When recently I agreed to present this paper, I set my secretary to work hastily cataloguing the articles about psychopharmacological drugs which have appeared in the past twelve months. She soon had over 500 articles, without including the foreign language literature. When I read Joseph Wortis's review in the January issue of the American Journal of Psychiatry,[11] I found he had listed 120 articles which he said he selected from about 1,000 available. When I scanned the 50 some abstracts in the 1960-61 *Year Book of Drug Therapy,*[2] there were only six references which duplicated the articles quoted by Joseph Wortis.

It soon became apparent that it would be impossible for me to present a reliable up-to-date review in this short period of time. It has not been possible for me to even read enough to more than guess at which articles are the most significant. My compromise has been to code the titles and select some samples from them. I, therefore, shall try to present some basic principles for evaluating the subject and guess at some of the patterns of progress ahead of us.

In my chapter review, "Drugs and Electroshock Treatment" in the 1960 volume of *Progress in Neurology and Psychiatry,*[10] I quoted Holt's 1959 paper[6] as follows: "After an initial decrease in the use of electroshock after introduction of tranquilizing and energizing drugs, electroshock has regained the ground lost and remains the speediest therapy for relief of the acute psychotic reactions, notably depression." He has assured me that recent developments have not significantly changed his opinion. A year ago the early reports on isocarboxazid, phenelzine, and nialamide were making the familiar early claims that they could largely replace ECT for depressions, but I expressed my skepticism at that time.

Before I comment on the recent reports about isocarboxazid, I would like to make a self-analysis regarding my resistance to the claims for these drugs. In the first place, I have worked out a system which is familiar to me, which gives me confidence that I have a high grade of economical treatment, which I can offer to a wide variety of my patients in my private office practice. This system involves a rapid survey of the presenting symptoms with the help of a self-scoring psychiatric scale for those who are mentally capable of scoring it. For those who have difficulty filling it out on their own, I can use the same form and fill in the information myself while questioning the patient for the details. I also give many of my patients the Minnesota Multiphasic Personality Inventory to fill out at home as an alternate source of information regarding their symptom profile. For most of my patients, I can collect enough information during the first interview to decide whether I want to continue for the time being on psychotherapy alone, or whether I want to start them right out on electrical treatment, either non-convulsive electrostimulation under sodium thiopental anesthesia (ESnc) or electroconvulsive therapy preceded by I.V. sodium thiopental (ECT).

More often than not I give ESnc first because it gives me important additional information. It reveals those patients who are ready to abreact and get relief from a discharge of their repressed feelings. It also quite reliably reveals those patients who show a trend to increased depression following the ESnc. Where the depression is obviously deep and the agitation presses for immediate action, ECT is given as the first treatment, but in many patients the issue is not as clear. The pattern of response to the ESnc is very helpful in deciding whether it is probably desirable to continue the ESnc or whether a switch to ECT is desirable. The patient is given the I.V. sodium thiopental in either case, and in most cases he is not informed ahead of time as to the difference in the treatments he may receive. When ECT is planned, the amount of sodium thiopental used is about two-thirds of the amount used for ESnc. The ECT is induced with an ascending current strength, manually con-

trolled, and then the tonic and clonic phases are splinted by continued stimulation at a level adjusted to the force of the patient's muscle contractions. Many patients are able to recognize afterwards that they have received a different treatment, but they are usually satisfied with the general statement, "Yes, I made it a little stronger today."

Often I prescribe a small amount of mild medication to take the edge off their symptoms while the main therapy is taking effect. My choices for this purpose have been vinbarbital gr. ss t.i.d. as needed or meprobamate 400 mg. t.i.d. or q.i.d. as needed, or plain Dexamyl, one tablet in the A.M. if necessary. If bedtime medication is called for, I usually prescribe vinbarbital gr. ss at h.s. if necessary. This small group of drugs has very few side effects in the doses prescribed. There is no loss of initiative and no hangover from them so that the progress of the patient is not confused by the medication.

With this program, I am troubled with very few complications and side effects. When the ECT has to be intensified, most patients soon comment on some spotty memory disturbances. This is practically the only side effect in this program that sometimes is annoying.

As you can see, any competing therapy has to offer a noticeable gain in the comfort of the patients, appreciably speed up the progress of the patients and not add significantly to the need of control studies to avoid new and hidden complications.

As I review the articles on isocarboxazid, I find myself in conflict. They sound good but the side effects, though labeled as minimal and reversible, are perplexing. It seems that if the dose is not raised above 30 mg. daily, the visible side effects are less common. However, there is agreement that approximately three weeks are needed to see whether the drug is going to be helpful, and then there is the expectation that the drug should be continued on lower maintenance dosage for several months to avoid relapse. In the meantime, there is no good index of over-all progress. In contrast, with the treatment program I have outlined above, both the patient and I can judge the level of progress with confidence that we are observing the level of the person's inner adjustment rather than just observing a drug reaction coating over an unknown core. Many patients express the feeling of not wishing to take pills week after week without being able to know from day to day whether they need them. Any medication which allays immediate symptoms is more understandable to the patient.

Let us examine more closely the side effects which have been reported for isocarboxazid. Carter[3] in treating 116 institutionalized mentally retarded patients with 10 to 30 mg. of isocarboxazid daily over a five to seven month period observed that five patients experienced an increase in grand mal seizures. This warns us that isocarboxazid is an analeptic and even in this dosage range may enhance a grand mal tendency. Dean[5] gives a generally favorable report for isocarboxazid, using 10 to 40 mg. daily for two weeks to three months, and continuing at that level or less for several months according to the patient's response. He reported on 47 patients treated in the office. However, he stated: "Three patients discontinued medication because of 'nervousness' and one was taken off the drug after two weeks because of orthostatic hypotension which responded to interruption of treatment and a subsequent reduction in dosage; one became constipated; two developed edema which was routinely managed with diuretics and reduction of dosage." This was a favorable report, but a drug which can produce that many complications is not going to be used by me in my set-up except in those cases where my regular routine is failing to get satisfactory results. Let us look further.

Kimbell and Pokorny[7] give a favorable report for isocarboxazid, saying, ". . . Marplan appears to be an effective, safe, and reasonably well-tolerated drug in the treatment of elderly, chronically depressed patients." However, they noted that a patient with a schizophrenic reaction became less depressed on isocarboxazid, but became more obviously schizophrenic with marked suspiciousness, delusional ideation and mild grandiosity. They also describe a 72-year-old white male whose mood improved with isocarboxazid, but who became dizzy and fell several times, one time causing a laceration on his forehead. This continued even at 10 mg. daily,

so the drug was discontinued. The dizziness and falling stopped, but his depressive symptoms returned.

Lathbury[8] states: "It was concluded that when administered to patients in certain categories, isocarboxazid is an extremely safe and effective antidepressant." However, he also stated: "Dizziness was easily managed if patients were cautioned against sudden changes of position, and advised to sit down for a moment until the attack passed."

I ask you, "Are we hypnotized by these drugs so that we make rosy claims for them at the same time we are honestly reporting the side effects?"

Yochelson[12] gives a strongly favorable report for isocarboxazid, emphasizing that it markedly reduced the need for ECT. He makes the interesting observation, that, in a case of combined psychic tension and depression, the depressive component was decreased and the psychic tension component was increased by the drug. Out of 36 patients in his study, isocarboxazid was discontinued in five because of increased psychic tension. What is the great value of a drug that, in an appreciable number of cases, enhances a grand mal tendency, or knocks the blood pressure down to hypotensive levels, or causes edema, or causes increased psychic tension, or enhances schizophrenic symptoms?

I would like to call your attention to the article by Cattell and Malitz[4] which rates some 50 drugs in this field on effectuality 1, 2, or 3 and on toxicity and side reactions A, B, and C. This is a realistic and sobering classification. The side effects are sufficiently formidable so that I feel I can use very few of the drugs profitably in my patients who are suitable for out-patient treatment. As an aside, it might be questioned whether, when the ideal symptomatic antidepressant is found, we would dare use it because of the almost inevitable addiction potentialities, even if only in terms of psychic dependency.

In all fairness, I want to point out how a different setup would reasonably influence one's judgment. I give all my treatments in my office. It is arranged so this is feasible and convenient. On the other hand, if a psychiatrist's program is to give all his electric treatments in a hospital or clinic at some distance from his office, he needs to rationalize the expense and inconvenience to his patient. In my set-up, the shift from one pattern of treatment to another is very easy. The only considerations are indications, and whatever changes in terms of time and chauffeuring are required. I see about 500 patients a year, only a small percentage of whom are for diagnosis only. The hazards of sodium thiopental have been adequately offset by care in technique. It is to be granted that this program does not take care of those patients who require hospitalization for reasons other than the treatments themselves.

There is a crying need among us which requires a vastly improved system for its solution. I know the foundations are being laid, but I have not had time yet to search out the details of progress. The question is, "Where can I send selected patients for better treatment than I can give them?" Certainly, I can send them to this famous hospital or that sanitarium—and what happens? They come back after a few weeks, having spent a considerable sum of money, but their treatment has been less definitive than mine and there is no added advice as to what is more likely to be a successful program for them.

We need to begin to think in terms of coding our information in ways which can be used in computer systems so that the rapid advances can be known and utilized. In my chapter review, I used the simple phrases ECT-resistant and ECT-yielding cases, and drug-resistant and drug-yielding cases. Obviously the drug-resistant and the drug-yielding cases must be broken down into the chlorpromazine-resistant and the chlorpromazine-yielding cases, or the perphenazine-resistant cases and the perphenazine-yielding cases, etc.

It is no longer simply a question of whether ECT is better or a particular drug is better. The case needs to be defined in a precise way and then by various tests and trials classified in terms of patterns of resistance and of yielding to various modalities. When I can send a patient to a research center and receive the patient back after a month with the prescription that this patient is an ECT-yielding case who is resistant to imipramine, for example, but yields favorably to trifluoperazine, but with a susceptibility to the following side-effects,

to be specified, then the expense incurred would be more worthwhile.

Another way this might work is that I could send certain coded information to a research center in Washington and receive back information as to which institutions are making special studies on this patient's type of problem. The counterpart of this would be that there would be movement of selected patients to various centers for special study and treatment in various categories. You may be amused at the idea that patients are going to be treated by Univac orders, but whether we like it or not, this is the path of the future.

Some will fall by the wayside, thinking that this is enough, but others will be masters of the new science, so that all the computers that can add to our classified knowledge will be combined with the best efforts in direct doctor-patient relationship in the treatment of the patient, the constructive use of transference, etc.

I am sorry that I cannot at this time give a detailed report on the comparative values of the many drugs which are being so intensively studied. The pace has outstripped me and will continue to outstrip all of us until we yield to the demands of progress and utilize the new methods of information retrieval. We are beset with competing prejudices and misconceptions which we need to help each other to overcome. For example, Joseph Wortis speaks of EST in the following terms, ". . . in spite of its crudity (EST) still is a quick and sure method for the relief of depressions." The attitude that electroconvulsive therapy was a crude method was already prevalent in 1944. As many of you know, I have been advocating the concept that electrostimulation is not a simple push-button modality, but really is a multiple modality with different techniques for different purposes. The refinements are continuing to be studied in certain areas.

Howard G. Alexander[1] has devised a technique of rapid treatment of schizophrenics. He starts the patients out on 5 mg. of trifluoperazine b.i.d. and simultaneously gives two ECT's daily, about one hour apart, until profound regression occurs, to the level of disorientation, marked retardation and in some cases, soiling. Then he switches to nonconvulsive electrostimulation for 20 secs. on alternate days for eight treatments. The nonconvulsive electrical stimulation rapidly relieves the confusion produced by the ECT. Twenty-one days after the treatment is started, 75% of his early schizophrenics are free of psychotic symptoms and are capable of accepting responsibility. Then he starts them on a rehabilitation program. He uses alternating current for both the ECT and the ESnc. He is enthusiastic about the synergism between his regressive electroshock therapy and the trifluoperazine. He gets results with this combination in patients who were resistant to regressive ECT alone and to trifluoperazine alone. Further study is needed to determine how much regression is necessary to obtain the desired results.

Weckowicz and Ward[9] made an excellent study of trifluoperazine in apathetic chronic schizophrenics. They coded their patients' behavior so that the reactions to the medication could be quantified in various categories. This is in line with what we need, namely, improved definition of the symptoms which respond favorably to a particular drug. I wish to strongly emphasize that there is a big difference in the program for patients who need to be hospitalized for treatment and those who are suitable for out-patient management.

Summary

Day after day, week after week, I treat psychiatric patients in my office with individualized, precisely differentiated techniques, using various modalities of relatively mild electrostimulation, accompanied by the minimal use of drugs. Surprisingly few of my patients require hospitalization. For the most part, they continue on the jobs they are on. My methods leave the patients in an alert, oriented state so that their progress can be evaluated from day to day and week to week. I am appalled when I read and hear about the complex and hidden side effects that accompany the use of so many of the new drugs widely heralded in psychopharmacology. It forces me to believe that my colleagues have not mastered the relatively simple methods of delicate and differential electrostimulation, combined with active psychotherapy, which make possible a high standard of therapy against which to compare the drugs. When a patient is sick

enough to require hospitalization, it becomes more reasonable to try out various treatments of increasing difficulty and of increasing hazard to attempt to turn the tide in cases which have not responded to the safer techniques. Personally, I am prejudiced against regressive treatment, but it may be necessary in some cases. The seductive enthusiasm for new drugs will undoubtedly continue to supply us with a continuous series of them. It seems to me that we shall need to resort to specialized methods of coding information and information retrieval to aid us in sorting out what to do for specified patients. Furthermore, we need to keep reminding ourselves that our immediate and our long range goals are not all the same, and these differences unconsciously load our biases in favor of or against various treatment methods.

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Isocarboxazid is available under the trademark Marplan, phenelzine under the trademark Nardil, nialamide under the trademark Niamid, meprobamate under the trademarks Miltown® and Equanil®, sodium thiopental as Pentothal® Sodium, vinbarbital under the trademark Delvinal®, chlorpromazine under the trademark Thorazine®, trifluoperazine under the trademark Stelazine®, perphenazine under the trademark Trilafon®. Dexamyl® is a combination of sulfate and amobarbital.

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Treatment of Depressive States with Amitriptyline

DOUGLAS BENNETT, M.D.*

The evaluation of new psychotropic drugs is beset with methodological difficulties. These have been described in the report of the World Health Organization Study Group on "Ataractic and Hallucinogenic Drugs," who stress the need for a more rigorous scientific approach to this problem.

When one is presented with a new psychotropic drug, there is much to be said for a preliminary study to decide on clinical grounds whether the drug appears to have any activity at all, its speed of action, which type of patient shows the best response to the drug, the side effects, and any toxic manifestations. The acceptance by patients of the drug, the effective dosage and the best method of administration must also be investigated.

The study I am reporting is designed to give a preliminary answer to some of these questions about amitriptyline. Controlled studies using precise methodology have been commenced but no results are available yet.

The patients studied were selected from the out-patient departments of two general hospitals, one in London and one in Surrey, and from a mental hospital outside London. They were selected for a variety of reasons; for their failure to respond to previous treatment, because their illness coincided with one's interest in the new form of treatment, and possibly (as the study proceeded) because they were thought likely, from experience already gained, to respond favorably to amitriptyline. While such selection may be biased, cases unlikely to respond were not outnumbered by favorable cases and random selection might well give similar results.

Seventy-four cases, 49 women and 25 men, were treated. Their ages ranged from 18 to 73 years. Diagnostically they were classified as depressed manic-depressive patients (50); involutional depression (5); neurotic depressions (18); epilepsy with depression (1). No schizophrenics were included.

All patients were given oral amitriptyline and the method of administration was standardized. Twenty-five mg. was given thrice daily for five days and the dose was then increased to 50 mg. three times a day. No patient was given doses in excess of 150 mg. a day. Only one patient had a tranquilizer in addition, but most patients were taking a barbiturate sedative at night. It is impossible, in this study (which has only been in progress six months) to draw firm conclusions as to the duration of treatment.

Response to treatment was rarely noted before the 10th or 14th day, and in only two cases was improvement noted before this time. In some patients, improvement was not noted until they had been on treatment for a month, and others showing partial improvement responded even more slowly.

Increase in appetite and weight often occurred, but seemed less marked than with the monoamine oxidase inhibiting drugs.

In the early stages of treatment, many patients complained of considerable drowsiness, which diminished as treatment continued, although the drug was on occasion abandoned by the patient for this reason.

In those cases showing a good response, early and dramatic improvement in sleeplessness resulted and many patients noted a feeling of relaxation.

The ability of some patients to reduce their night sedatives after only a month's treatment was unique in my experience of the treatment of depression.

Transient episodes of relief of depressive feelings, lasting minutes or an hour, were noted by intelligent and observant patients during the first week of treatment and seemed to augur well for the success of treatment.

A few patients showed marked objective improvement in their condition for some time before they would admit to any subjective feeling of relief. Only one patient responded well to treatment, and then, following the reduction of the dose to 100 mg. amitriptyline daily, relapsed and failed to respond again to treatment. Four patients developed hypomania of varying degrees. The "swing-over" to hypomania occurred quite suddenly and with little warning in two cases. In two other patients prompt action

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in stopping amitriptyline and giving chlorpromazine prevented the development of more serious symptoms. I am not yet certain how to avoid this difficulty in view of the apparent absence of warning signs.

These were not unduly troublesome and much less marked than those occurring in treatment with imipramine. The commonest were dry mouth and drowsiness, excessive perspiration and constipation. Blurring of vision occurred, but not commonly. Nausea was noted, as was heartburn. Heartburn was complained of by three patients. I have not seen it mentioned previously.

There is a tendency for the side effects to diminish as treatment continues.

Of the eight patients who discontinued treatment six complained bitterly of tiredness and drowsiness.

Postural hypotension and toxic effects on the liver or blood were not noted.

Results

Of the 74 patients 34 (46%) were definitely improved with the total disappearance of depressive symptoms and a return to normal activity, while 17 (23%) were partially improved with a reduction in some or all depressive symptoms short of total disappearance. Fifteen patients (21%) showed no improvement, and eight (10%) discontinued treatment.

Forty-four percent of the depressed manic-depressives, 80% of involutional depressions, and 33% of neurotic depressions, were definitely improved.

Among those who showed definite improvement, the most interesting finding was that 11 had failed to respond satisfactorily to previous treatment with electroplexy; five, however, had responded equally well to previous electroplexy. Fifteen responded better to amitriptyline than to other antidepressive drugs, while one had responded as well to another drug. Four had had no previous treatment.

Of those who did not improve with amitriptyline, five improved with electroplexy, three with other antidepressive drugs, while four have not been improved by any form of treatment.

Depressed manic-depressives who were in a mental hospital did less well than out-patient cases presumably because they were more ill and had been depressed longer. Two such patients, however, responded dramatically.

I could not, on the basis of this study, persuade myself that agitated depressives did either better or less well than retarded depressives.

Conclusions

There seems to be no reason to doubt that amitriptyline is an effective antidepressive drug. If my results seem surprisingly good, this may in part be determined by the selection of cases. Several cases had, however, been known to me for periods of up to six years and had proved refractory to all other forms of treatment. It appears to be most effective in the treatment of manic-depressive depressions and involutional depressions of mild to moderate severity. It is also effective in some neurotic depressions and some more severely depressed manic-depressives.

Side effects are not unduly troublesome, but intense drowsiness early in treatment leads some patients to abandon the drug.

The relief of insomnia and the relaxation noted by many patients is one of the more dramatic effects of amitriptyline. It can be given effectively to out-patients without difficulty but its potency, as shown by the tendency of some patients to develop hypomania, demands that patients treated out of hospital should be kept under frequent observation.

The only disadvantage of oral treatment in more severely ill patients is the time taken to achieve a satisfactory response.

Doses of more than 150 mg. daily by mouth are not necessary. I have not been using the drug long enough to make any useful comment on the necessary duration of treatment.

Amitriptyline is available under the trademark Elavil®, chlorpromazine under the trademark Thorazine®, imipramine under the trademark Tofranil®.